Screening and Diagnosis of Prediabetes and Diabetes:

Epidemiologic Research to Inform Prevention

by
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A dissertation submitted to Johns Hopkins University in conformity with the requirements for the degree of Doctor of Philosophy

Baltimore, Maryland
March 2018

Abstract

This dissertation is an epidemiologic query designed to address important questions related to screening and diagnosis of prediabetes and diabetes. We used data from the Atherosclerosis Risk in Communities (ARIC) Study, an ongoing community-based cohort initiated in 1987, to assess four main aims.

First, we examined trajectories of kidney function by diabetes status. Persons with diagnosed diabetes declined almost twice as rapidly as persons without diabetes (-2.5 ml/min/1.73 m^2 per year [95%CI, -2.6, -2.4]; -1.4 ml/min/1.73 m^2 per year [95%CI, -1.5, -1.4], respectively). Those with undiagnosed diabetes, likely early in the disease course, experienced relatively little short-term average decline, but declined in the long-term. This brief period of stagnation suggests potential hyperfiltration.

Second, we compared the prognostic performance of five definitions of prediabetes in use by international organizations. Prediabetes prevalence ranged widely depending on the definition (9% to 38%), but all definitions identified persons at high-risk for clinical outcomes. Fasting glucose 100-126 mg/dL was more sensitive for clinical complications, while HbA1c 5.7-6.4% and 6.0-6.4% were more specific and provided modest statistically significant improvements in risk discrimination.

Third, we conducted a diagnostic testing study, comparing 1,5-anhydroglucitol (1,5-AG), a less burdensome test, to 2-hour glucose for identification of hyperglycemia. Their concordance was low and, while specific for high glucose levels, 1,5-AG missed many people with elevated 2-hour glucose.

Finally, we compared the prospective associations of 1,5-AG and 2-hour glucose with risk of future clinical outcomes. Low levels of 1,5-AG were associated with risk of future outcomes, but not as strongly as 2-hour glucose.

Given the proven approaches to prevent progression to diabetes and reduce incidence of its complications, our data reinforced the need for prediabetes and diabetes screening and diagnosis, with consistent identification of individuals to inform public health planning. We proposed further understanding hyperfiltration and exploring new ways to optimize prediabetes definitions. While 1,5-AG does not appear to substitute for 2-hour glucose and may have limited screening utility, additional research is needed to assess it as a measure of glycemic control in persons with diagnosed diabetes. Our research directly informs important next steps to promote prevention of diabetes and its complications.

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Acknowledgements

This work was made possible with valuable contributions from many supportive people along the way. First and foremost, I thank my adviser Dr. Elizabeth Selvin for providing incredible scientific opportunities, challenging me to learn and grow, and supporting me continually. Dr. Selvin's guidance during this dissertation and my PhD process proved invaluable. I thank Dr. Morgan Grams for providing insightful mentorship and guidance throughout the process and for being so patient with my learning.

Dr. Josef Coresh and Dr. Richey Sharrett provided comments and asked key questions to push this work forward for which I am grateful. I also thank the many other faculty members who served on my exam committees or attended presentations and provided feedback and encouragement. I acknowledge the incredible contributions of my collaborators on these projects, whose ideas and insights improved the science. I would also like to extend my thanks to the faculty and trainees at the Welch Center for Prevention, Epidemiology, and Clinical Research for their collaboration and collegiality. Additionally, I am grateful for my PhD cohort, who shared their diverse perspectives, served as a sounding board for science, and provided immense moral support.

There were also many people who guided me before beginning this degree. I am grateful to my mentors at University of Pennsylvania and Booz Allen Hamilton who helped me discover my love for epidemiology and nurtured my confidence to pursue it: Dr. Peter Kanetsky, Dr. Ann Greene, Dr. Anita Cattrell, and Ms. Jeni Fan. I thank my family and friends for continually encouraging, supporting, and believing in me. Finally,

I thank and dedicate this dissertation to my Gma and Gpa, who are a continuous source of love, inspiration, and joy.

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List of Acronyms

1,5-AG	1,5-anhydroglucitol
ADA	American Diabetes Association
ACR	Albumin-to-creatinine ratio
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ARIC	Atherosclerosis Risk in Communities
BCM	Baylor College of Medicine
BMI	Body mass index
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
cNRI	Continuous net reclassification improvement
CV	Coefficient of variation
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DECODE	Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe
eGFR	Estimated glomerular filtration rate
ERFC	Emerging Risk Factors Collaboration
FP	False positive
FN	False negative
h	Hour (e.g., 2 h or 10 h)
HbA1c	Hemoglobin A1c
HDL	High density lipoprotein
ICD-9	International Classification of Disease, Ninth Revision
IEC	International Expert Committee
KIDGO	Kidney Disease Improving Global Outcomes
NHANES	National Health and Nutrition Examination Survey
NGSP	National Glycohemoglobin Standardization Program
NPV	Negative predictive value
OGTT	Oral glucose tolerance test
PPV	Positive predictive value
ROC	Receiver operating characteristic
SGLT	Sodium-glucose co-transporter
TP	True positive
TN	True negative
UMN	University of Minnesota
USRDS	United States Renal Data System
WHO	World Health Organization
+LR	Positive likelihood ratio
-LR	Negative likelihood ratio

Introduction

Diabetes and prediabetes are major global public health challenges. Early identification provides opportunities to prevent diabetes and its associated complications. Thus, this dissertation focused on issues related to screening for prediabetes and diabetes. Specifically, we provide evidence that reinforces the need for diagnosis by quantifying trajectories in kidney function over time by diabetes status, and data to inform tailored screening and diagnosis strategies by addressing controversies in prediabetes screening, and evaluating whether an emerging biomarker of hyperglycemia, 1,5-anhydroglucitol, can be used for diabetes screening.

Diabetes and prediabetes: a pressing public health problem

Diabetes is a rising global problem, as the prevalence in the last several decades have been stable or increasing in every country[1]. In the United States, 11% of people are living with diabetes (25.5 million), and ~2.8 million of those cases are undiagnosed[2]. In general terms, diabetes is a disease characterized by chronic hyperglycemia that results from insufficient insulin secretion and/or action. The two most common forms of diabetes, type 1 and 2, have different disease etiologies. Type 2, accounts for approximately 95% of the diabetes in the U.S. and is the focus of this dissertation[3]. Type 2 diabetes is often characterized by insulin resistance, whereas type 1 diabetes is associated with insufficient or lack of insulin secretion. In the absence of diabetes, insulin is secreted by the beta cells in the pancreas when blood glucose is high to promote the uptake of glucose into cells. Cellular resistance to the effects of insulin occurs when the action of insulin is insufficient, meaning insulin is still being secreted by the pancreas but

the uptake of glucose into cells is diminished, and higher concentrations of glucose remain in the blood[4].

Common risk factors for diabetes include age, race/ethnicity, family history of diabetes, obesity, hypertension, low HDL cholesterol, high triglycerides, physical inactivity, dietary factors, and, in women, a previous diagnosis of gestational diabetes[5]. Diabetes is strongly associated with increased micro- and macrovascular complications including retinopathy, nephropathy, and neuropathy, coronary heart disease, ischemic stroke, and peripheral arterial disease[6]. Indeed, persons with diabetes are at an approximately 2-4 times higher risk of cardiovascular disease than those without diabetes[7]. The public health burden of diabetes is substantial. In the U.S., diabetes is now the leading cause of blindness and end stage renal disease[8,9]. However, despite the well-established relationship of diabetes as a risk factor for chronic kidney disease and end stage renal disease, the contribution of diabetes to kidney function decline over time in the general population is largely uncharacterized.

The management of diabetes and its associated complications result in excess healthcare burden and medical costs. In the U.S. in 2014 alone, persons with diabetes were hospitalized at a rate of 327.2 (95% CI, 311.3, 343.1) per 1,000 and admitted to the emergency department at a rate of 648.9 (95% CI, 600.0, 696.9) per 1,000[3]. In 2012, total estimated cost (direct and indirect) of diagnosed diabetes in the U.S. was $245 billion[3].

Persons who are at high risk for diabetes are often termed as having "prediabetes", a state characterized by hyperglycemia but where blood glucose concentrations do not yet meet the diagnostic threshold for diabetes. The prevalence of prediabetes varies substantially by the definition used, and in the U.S. prevalence

estimates range from 12-29% of the total adult population[10]. Among people with prediabetes, approximately 5 to 10% progress to diabetes annually[11]. Like diabetes, prediabetes is associated with adverse microvascular and macrovascular outcomes[12,13].

Importance of screening for prediabetes and diabetes

It is important to consider whether screening in asymptomatic individuals for a particular disease is appropriate. Screening is indicated for those diseases that are burdensome and treatable and where available screening tests are acceptable (low patient burden) and able to effectively separate those with and without the disease. With these principles taken together, **Table 1** describes objective characteristics for successful screening outlined by Riegelman (2005)[14] that have been adapted to demonstrate the need and ability to screen for prediabetes and diabetes. In the context of hyperglycemia, screening is particularly important because prediabetes and diabetes are associated with increased microvascular and macrovascular complications and all-cause mortality; further, treatment and improvement in glycemic control can reduce microvascular complications[15–19], and perhaps macrovascular complications[20,21]; approaches exist to prevent progression from prediabetes to diabetes[22–24]; the tests used for diagnosis can identify those with the disease[25]; and screening can be conducted with a minimally invasive blood draw.

Importantly, the typical first line intervention for both prediabetes and diabetes is lifestyle management, which includes nutrition management, regular physical activity, and weight loss and maintenance[26]. Nutritional recommendations often suggest a healthy low-calorie diet, physical activity recommendations typically emphasize at least 150 minutes of moderate to vigorous activity per week, and weight loss and maintenance is

aimed at 7% of body weight[26]. These general recommendations are tailored to individual needs. In the general U.S. population, meeting these goals without intervention is rare. One study conducted in NHANES demonstrated that only 3.1% of adults without diagnosed diabetes met dietary, physical activity, and weight loss/maintenance goals for reduction of type 2 diabetes risk[27]. Screening can help identify those at risk and presents an opportunity for intervention among the individuals who may benefit.

The 2015 U.S. Preventative Services Task Force Final Recommendation Statement for Screening for Abnormal Blood Glucose and Type 2 Diabetes Mellitus state that screening should be conducted every 3 years in asymptomatic adults aged 40-70 years who are overweight or obese[28]. The recommendation also notes that clinicians should consider screening at earlier ages for persons with one or more additional risk factors for diabetes. The American Diabetes Association, however, recommends screening in all asymptomatic adults 45 years or older or adults of any age who are overweight or obese and who have at least one diabetes risk factor[5]. The Canadian Task Force on Preventative Health Care convened in 2012 recommends yet another approach. They suggest that adults with low or moderate risk of future diabetes determined by a risk score should not be screened. Using the same risk score, they suggest adults at high risk should have their Hemglobin A1c (HbA1c) measured every three to five years, and those at very high risk should have their HbA1c measured every year[29]. The National Institute for Health and Clinical Excellence also relies on a risk score to identify high-risk individuals who should be screened for diabetes using a blood test[30]. Despite differences in specific screening recommendations, there is broad agreement that screening for diabetes and prediabetes is important.

Guidelines organizations have relied largely on observational data to inform screening recommendations. Evidence from trials and intervention studies is scarce due to the complexity, ethical issues, and the substantial sample size, resources, and follow-up time needed to evaluate effects on clinical endpoints. Nonetheless, there have been two randomized control trials that assessed whether screening for diabetes in asymptomatic individuals reduces mortality; these found either no or a small benefit[31,32]. These trials were limited by improvements in treatment in the control group over time, along with the low prevalence of screen-detected diabetes among their participants, and lower than expected event rates. These studies illustrate the major challenges in conducting randomized control trials of screening questions. Therefore, rigorous observational studies and epidemiological evidence is critical.

Approaches to screening and diagnosis of prediabetes and diabetes

Diabetes screening approaches have evolved over time[33]. Identifying persons with diabetes dates back as far 1500 BC, although the first known "screening tests"—involving the tasting of urine—were recorded in the first and second centuries AD[34]. Testing urine, although the methods to do so have evolved, continued as the primary means of diagnosis for hundreds of years[34]. In the late eighteenth century, work done by Matthew Dobson, an English physician, characterized diabetes as a system disorder and found sugar in both urine and blood[7,34]. This advancement laid the foundation for blood tests to diagnosis diabetes.

In 1913, Ivar Christian Bang, a chemistry professor at the University of Lund in Sweden, developed a method to quantify the amount of glucose in the blood[35]. This advancement, paired with the discovery in the same year by A.T.B. Jacobsen, who

determined that ingestion of carbohydrates results in fluctuations in blood glucose, set the stage for measuring blood glucose following a carbohydrate challenge[35]. The development of the glucose tolerance test is attributed to Jerome Conn in 1940[36].

In 1965, the World Health Organization published a report from an expert committee which recommended using laboratory criteria for the diagnosis of diabetes and included the glucose tolerance test and fasting glucose[37]. This was followed by the 1979 report from the National Diabetes Data Group which formalized diabetes classification and recommended the use of fasting glucose (≥140 mg/dL) or 2-hour glucose following a 75-g oral glucose tolerance test for diagnosis (≥200 mg/dL)[38]. It also established impaired glucose tolerance as a 2-hour glucose ≥140 mg/dL and <200 mg/dL when fasting glucose <140 mg/dL; and normal glucose levels as fasting glucose <115 mg/dL and 2-hour glucose <140 mg/dL. A lot of these developments were made possible by the work of Dr. Harry Keen—often considered a "father" of diabetes epidemiology—who was a member of the committee. Keen, along with Dr. Kelly West, championed screening for diabetes based on the prevalence of complications in asymptomatic persons with diabetes[39,40]. Given their findings and results of other early studies, the cut points for all continuous biomarkers used in guidelines were largely based off their relationship with microvascular outcomes, especially the prevalence of retinopathy, given its specificity to diabetes[25].

The clinical cut-points outlined by the National Diabetes Data Group remained in use until 1997 when the American Diabetes Association lowered the cut-point for diabetes diagnosis for fasting glucose from 140 mg/dL to 126 mg/dL (impaired fasting glucose: 110-126 mg/dL) based on an expert committee report[41], followed by World

Health Organization in 1999[42]. In 2003, American Diabetes Association again changed cut-points, this time for impaired fasting glucose from 110 mg/dL to 100 mg/dL[43].

In 2009, for the first time, an International Expert Committee recommended HbA1c for diagnosis[44]. At this time, HbA1c had been used for decades as the standard measure of chronic hyperglycemia to assess glycemic control among persons with diabetes. The 2009 report was published over 40 years after the glycation of HbA1c among persons with diabetes was discovered by Samuel Rahbar, an Iranian physician, and over 15 years after the Diabetes Control and Complications Trial (DCCT) demonstrated associations between HbA1c and diabetes complications[6,45]. This delay in uptake following the DCCT was partly due to the need to standardize the HbA1c assay, a problem addressed by the National Glycohemoglobin Standardization Program (NGSP). In 2010, American Diabetes Association guidelines formally recommended the use of the HbA1c test for diagnosis[46].

Today, prediabetes (impaired glucose tolerance, impaired fasting glucose, and impaired glycated hemoglobin) and diabetes continue to be diagnosed by fasting glucose, 2-hour glucose, and/or HbA1c. A description of each biomarker and the construct it represents is listed in **Table 2**. Currently, international organizations generally agree on the tests and cutoffs that should be used to identify persons with diabetes. However, international guideline groups have not reached consensus on the thresholds for prediabetes (**Table 3)**. While there are three different definitions of diabetes, any of which can be used for diagnosis, there are five different definitions of prediabetes currently in use, with inconsistent recommendations for their use by guidelines organizations. Further, since prediabetes or 'borderline diabetes' was first introduced in

the 1960s by Dr. Harry Keen its necessity has been debated. Some experts claim that prediabetes is an unnecessary label that can lead to "over-medicalization" and which serves to enhance the bottom line of pharmaceutical companies[47,48]. However, others recognize that since glucose levels—even below the threshold for a diagnosis of diabetes—are associated with increased risk of major complications and the disease process is continuous, identifying and categorizing persons early in the disease process is important to prevent diabetes. The optimal definition of prediabetes, approaches to the patients with prediabetes, and insurance coverage for lifestyle interventions and other treatments in persons with prediabetes remain controversial.

Current guidelines and recommendations take into consideration the limitations of each biomarker used for diagnosis of diabetes and identification of persons with prediabetes (**Table 4)**. Two-hour glucose, in particular, has fallen out of favor—especially in the U.S.—as a first line screening or diagnostic test given its high burden on the patient and healthcare system. Nonetheless, given its long history and place in diagnosis of diabetes, the two-hour post-challenge glucose test is still considered as an important "gold standard" for diabetes diagnosis.

1,5-anhydroglucitol: A promising alternative to 2-hour glucose?

1,5-anhydroglucitol (1,5-AG) is a biomarker that has received recent interest as a novel biomarker of hyperglycemia. The biology of 1,5-AG is distinct from either glucose or HbA1c. It is a six-carbon monosaccharide that differs from glucose by one fewer hydroxyl group[49]. In the absence of hyperglycemia, the amount of circulating 1,5-AG is thought to remain at steady-state[50]. 1,5-AG is largely obtained from dietary sources, although it is believed that there may be a small amount of 1,5-AG synthesized in the

liver and possible that there is a some degree of degradation[50]. Some 1,5-AG is excreted in urine even when blood glucose levels are normal, but it is approximately similar to the amount ingested and synthesized[50]. These inputs and outputs of 1,5-AG result in a relatively neutral exchange and constant pool in the body in the absence of hyperglycemia. Among healthy individuals, the reference intervals reported by the U.S. assay manufacturer, GlycoMark™ (Glycomark Inc, Winston-Salem, NC), are 10.7 to 32.0μg/mL in males, and 6.8 to 29.3μg/mL in females[51].

In periods of hyperglycemia exceeding the renal threshold for glucose (blood glucose concentrations >~160-180mg/dL), given their molecular similarity, glucose and 1,5-AG compete for reabsorption in the proximal tubule of the kidney, accelerating urine excretion and lowering the amount of circulating 1,5-AG in plasma. Thus, low concentrations of 1,5-AG in plasma reflect recent high blood glucose levels. After a period of hyperglycemia where the pool of 1,5-AG is decreased, 1,5-AG is thought to recover at rate of 0.3 μg/mL per day[52].

There is some evidence to suggest there may be a number of factors that influence the absolute amount of 1,5-AG, which may be particularly relevant in the absence of hyperglycemia. Dietary sources vary greatly in their 1,5-AG content[50,53]. For example, soybeans have particularly high amounts of 1,5-AG, followed by rice, noodles, bread, and beef[50]. Beyond 1,5-AG content in foods, a recent study demonstrated that diet may directly influence 1,5-AG serum concentrations[54]. Because of the interplay of 1,5-AG and the kidneys, 1,5-AG may not be reliable in persons with chronic kidney disease or persons taking medications from the sodium-glucose co-transporter 2 (SGLT2) drug class[55–57]. Additionally persons with liver disease have been shown to have low 1,5-AG

values regardless of glucose level[58]. Other factors that may impact interpretation of 1,5-AG include pregnancy or consumption of certain Chinese herbal supplements[49,51,57].

1,5-AG was first detected and characterized in plants in 1888, followed by humans in 1972[49]. In the early 1980s, differences in 1,5-AG concentrations among those with and without diabetes were observed[51]. Today, assays have been developed that allow measurement of 1,5-AG concentration in serum or plasma. An assay developed in Japan and in use since 1991, is marketed as GlycoMark™ in the United States and is one of the leading 1,5-AG assays. GlycoMark™ measures 1,5-AG using a two-step enzymatic method and was approved by the Food and Drug Administration for use in 2003[49,57]. There are several other 1,5-AG assays including the Determiner-L 1,5-AG (Kyowa Medex; Tokyo, Japan) which has been shown to be similar to GlycoMark™, with a mean difference between the two assays of 0.4μg/mL in a community-based population[59]. A third method, the Cusabio Human 1,5-AG ELISA Kit, has been sparsely used in the literature.

1,5-AG is a non-fasting test and studies have suggested 1,5-AG may have utility in the setting of diagnosed diabetes to identify short-term glycemic changes, inform therapeutic decisions to minimize glycemic variability, and provide complementary information to HbA1c. The potential utility of 1,5-AG to provide information on short-term monitoring of blood glucose largely stems from a trial of the GlycoMark™ assay which demonstrated that 1,5-AG changed quickly (~2 weeks) in response to medications that lowered blood glucose[60], suggesting 1,5-AG could be used to monitor short-term changes in glucose control. Dungan et al demonstrated the ability of 1,5-AG to provide information for therapeutic decisions among persons with diabetes by utilizing

continuous glucose monitors and comparing changes in average glucose to HbA1c and 1,5-AG. They showed that for patients with similar HbA1c, those experiencing more glycemic excursions had lower 1,5-AG[61]. This suggests that 1,5-AG could identify patients experiencing postprandial glucose that may benefit from a different treatment regimen. Although, it is worth noting, that there is no evidence to-date to suggest that changes in treatment based on 1,5-AG improve clinical outcomes. Studies that have assessed the relationship of 1,5-AG and outcomes have shown that in the setting of diabetes, 1,5-AG predicts adverse outcomes beyond HbA1c[62,63]. This aligns with the literature that postprandial glucose is an independent risk factor for macrovascular complications.

There have been very few studies of 1,5-AG in persons without a diagnosis of diabetes, although there is a small literature that suggests that 1,5-AG might have utility for diabetes screening[64–66]. Because testing for 1,5-AG is simple and minimally invasive (single serum or plasma blood sample) and fasting is not required, 1,5-AG is of substantial interest as a potential alternative to the more burdensome oral glucose tolerance test. Given its attractive test properties and low coefficient of variation (ranging from 1.3-5.7%) – it is worth understanding whether 1,5-AG has utility for diabetes screening[51,67].

Study Aims

This dissertation was intended to tackle major questions related to screening for hyperglycemia by investigating the following specific aims:

Aim 1. To characterize trajectories of kidney function over time by diabetes status.

Aim 2. To compare the prevalence and prospective associations of different definitions of prediabetes with incident diabetes, chronic kidney disease, cardiovascular disease, peripheral arterial disease, and all-cause mortality.

Aim 3. To conduct a diagnostic testing study to evaluate the performance of 1,5-AG compared to 2-hour glucose to detect undiagnosed diabetes.

Aim 4. To compare the prospective associations of 1,5-AG and 2-hour glucose with incident diabetes, cardiovascular disease, and all-cause mortality among persons without diabetes.

Dissertation Data Source

The analyses in this dissertation were conducted using data from the Atherosclerosis Risk in Communities (ARIC) Study. The ARIC Study is a community-based cohort, initiated in 1987-1989 with 15,792 participants[68]. The study recruited participants from four communities in the United States (Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and suburban Minneapolis, Minnesota), collecting anthropometrics, blood samples, and self-report data at study visits. To date, there have been six study visits (1987-89, 1990-92, 1993-95, 1996-98, 2011-13, 2016-17), and a seventh is planned (2018-19).

For this dissertation, in collaboration with colleagues at the Baylor College of Medicine, 1,5-AG was measured in stored plasma samples collected from 11,656 participants during the fourth visit (1996-98). These new measurements presented a unique opportunity for comparison to the 2-hour glucose; since the fourth visit was the only time the oral glucose tolerance test protocol was administered during the ARIC study.

In order to utilize the new Visit 4 measurements, aligning the values with 1,5-AG measurements at other ARIC study visits (Visits 2 and 5), which were conducted in serum samples at the University of Minnesota, was necessary. To correct for lab and methodological differences, we designed and conducted a calibration study at the Baylor College of Medicine using stored samples from the fifth study visit (2011-2013). Lab differences were addressed by comparing measurements of 1,5-AG in University of Minnesota serum samples from visit 5 to new measurements of 1,5-AG conducted at the Baylor College of Medicine laboratory in different serum aliquots from the same participants (n=50). Methodological differences were then addressed by comparing plasma samples from Baylor College of Medicine (n=200) to serum samples from University of Minnesota. This process aligned the new Visit 4 1,5-AG measurements with previous measures at the second and fifth study visits and is further detailed in the *Methodological Supplement*. ARIC is a rich source of data that provides the information, sample size, and general population necessary to answer the clinical questions outlined for this dissertation.

Dissertation Structure

This dissertation has four chapters, one per aim, a conclusion, and methodological supplement. Each chapter is formatted as a publishable manuscript. *Chapter 1* quantifies the contribution of diabetes to kidney function decline over 25 years. *Chapter 2* compares the 5 different definitions of prediabetes and their associations with future adverse outcomes and was published in *Lancet Diabetes and Endocrinology*[69]. *Chapter 3* assesses the concordance of 1,5-AG and 2-hour glucose to identify undiagnosed diabetes in a community-based population. *Chapter 4* examines the associations of 1,5-AG and 2-hour

glucose among those without diagnosed diabetes with risk of future adverse outcomes. The *Methodological Supplement* details the statistical calibration of the data necessary before using it in analyses. Finally, the *Conclusion* summarizes the findings and outlines next steps for this research.

Table 1. Characteristics for successful screening by Reigelman (2005)[14] adapted to demonstrate the ability to successfully screen for diabetes and prediabetes

Construct	Characteristic	Application	
		Diabetes	**Prediabetes**
Disease	Associated with burden	Increased microvascular and macrovascular complications and all-cause mortality	Increased microvascular and macrovascular complications and all-cause mortality
	Early identification can improve outcomes	Glycemic control can reduce microvascular complications,[15–19] and perhaps macrovascular complications[20,21]	Early intervention through lifestyle or pharmacological intervention can reduce progression to diabetes[22–24]
Screening test	Feasible to identify participants with disease	2-hour glucose, fasting glucose, and HbA1c separate those with and without chronic hyperglycemia[25]	2-hour glucose, fasting glucose, and HbA1c separate those with and without chronic hyperglycemia[25]
	Acceptable and efficient	Fasting or non-fasting blood draw depending on biomarker	Fasting or non-fasting blood draw depending on biomarker

Table 2. Biomarkers of hyperglycemia used for diagnosis of prediabetes and diabetes and the glycemic constructs they represent

Biomarker	Biological definition	Glycemic construct
2-hour glucose following 75-g glucose tolerance test	Circulating blood glucose following a glucose challenge	Post-prandial glycemic excursions
Fasting glucose	Circulating blood glucose level after a fasting period	Glucose homeostasis
Hemoglobin A1c	The proportion of hemoglobin that has been glycated	Average glycemia over the previous 2-3 months

Table 3. Current definitions in use for diagnosis of prediabetes and diabetes

Biomarker	Organization	Definition	
		Diabetes	Prediabetes
2-hour glucose following 75-g glucose tolerance test	American Diabetes Association	≥200 mg/dL	≥140 mg/dL & <200 mg/dL
	World Health Organization		
Fasting glucose	American Diabetes Association	≥126 mg/dL	≥100 mg/dL & <126 mg/dL
	World Health Organization		≥110 mg/dL & <126 mg/dL
HbA1c	American Diabetes Association	≥6.5%	≥5.7% & <6.5%
	World Health Organization		--
	International Expert Committee		≥6.0% & <6.5%

Table 4. Limitations of current biomarkers used for diagnosis of prediabetes and diabetes

Limitation	Biomarker		
	2-hour glucose	Fasting glucose	HbA1c
Requires fasting	✓	✓	
Higher patient burden	✓		
Affected by recent activity, acute illness, or stress	✓	✓	
Higher intra-individual variability	✓	✓	
Pre-analytic issues	✓	✓	
Affected by alterations in red cell turnover			✓
More common assay interferences			✓
Whole blood required			✓
Cost			✓

Chapter 1. Diabetes and trajectories of estimated glomerular filtration rate: a prospective analysis of the Atherosclerosis Risk in Communities study

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Abstract

Objective. People with diabetes are at high risk for adverse kidney outcomes, including end-stage renal disease. To better characterize kidney disease development in persons with and without diabetes, we quantified trajectories of decline in estimated glomerular filtration rate (eGFR) in a community-based cohort with up to four measures of creatinine from 1987 to 2013.

Research Design and Methods. Among 15,517 participants in the Atherosclerosis Risk in Communities (ARIC) Study, we classified participants as having no diabetes, undiagnosed diabetes, and diagnosed diabetes at baseline (1987-89). We used linear mixed models with random intercepts and slopes to quantify decline in eGFR by diabetes status.

Results. Overall, the adjusted mean decline in eGFR among participants without diabetes at baseline was -1.4 ml/min/1.73 m^2 per year (95% CI, -1.5, -1.4); and with diagnosed diabetes, was -2.5 ml/min/1.73 m^2 per year (95% CI, -2.6, -2.4). Compared to participants without diabetes, participants with undiagnosed diabetes had higher baseline eGFR (adjusted difference, 2.3 ml/min/1.73 m^2 [95% CI 1.1, 3.4]) and slower eGFR decline over the first three years (difference, 0.4 ml/min/1.73 m^2 per year [95% CI, 0.1, 0.8]), but they had faster relative decline over the full study period (difference, -0.4 ml/min/1.73 m^2 per year [95% CI, -0.5, -0.3]). Among participants with diagnosed diabetes, steeper eGFR

decline was observed among African-American participants as well as those with *APOL1* risk genotype, systolic blood pressure ≥140 mmHg, those on insulin, and those with HbA1c ≥9%.

Conclusions. In summary, diagnosed diabetes was a strong risk factor for eGFR decline over a 26-year period, as was undiagnosed diabetes after an initial period of relatively little average eGFR decline. Steeper declines were seen in those with diagnosed diabetes and modifiable risk factors including higher systolic blood pressure and HbA1c, suggesting factors that should continue to be targeted for prevention of chronic kidney disease.

Introduction

Diabetes mellitus is increasingly prevalent worldwide[1,2] and is associated with high mortality and morbidity, including adverse kidney events. Diabetes is among the strongest common risk factors for end-stage renal disease, and in industrialized countries diabetes contributes to approximately 50% of cases[3]. Less is known about the pattern of kidney function decline associated with diabetes that precedes end-stage renal disease.

Identifying patterns of estimated glomerular filtration rate (eGFR) decline could inform monitoring practices for people at high risk of chronic kidney disease progression. A better understanding of when and in whom eGFR decline occurs would be useful for the design of clinical trials, since eGFR decline greater than 30% is now often used as a surrogate endpoint for chronic kidney disease progression[4]. Trajectories among persons with diabetes are of particular interest because of the possibility for early intervention and the prevention of chronic kidney disease development. However, eGFR trajectories among persons with new diabetes may be complex, due to the hypothesized period of

"hyperfiltration" whereby GFR increases, followed by progressive, rapid decline[5].

Using data from the Atherosclerosis Risk in Communities (ARIC) Study, an ongoing prospective community-based cohort of over 15,000 participants initiated in 1987 with serial measurements of creatinine over 26 years, our aim was to characterize patterns of eGFR decline associated with diabetes, to identify demographic, genetic, and modifiable risk factors within the population with diabetes mellitus that were associated with steeper eGFR decline, and to assess for evidence of early hyperfiltration.

Methods

Study Population

The ARIC study is comprised of 15,792 participants from four U.S. communities (Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland)[6]. Six study visits have been completed to date. We included data from the four visits with creatinine measurements (Visit 1 1987-89 (serum), Visit 2 1990-90 (serum), Visit 4 1996-98 (plasma), and Visit 5 2011-13 (serum)). Institutional review boards at each site approved the study and all participants provided informed consent.

Of the 15,792 participants who attended the first visit, we excluded those who had eGFR $\leq$15 ml/min/1.73 m^2 or end-stage renal disease at baseline (Visit 1, n=25), those not black or white race or black from the Minnesota or Maryland sites (n=103), and who were missing eGFR measurements (n=147), resulting in 15,517 participants in our study population.

Diabetes Assessment

Diabetes status was assessed at Visit 1 (baseline) and categorized as no diabetes,

undiagnosed diabetes, and diagnosed diabetes. Undiagnosed diabetes was defined as a fasting glucose ≥126 mg/dL or non-fasting glucose ≥200 mg/dL without medication or physician diagnosis. Diagnosed diabetes was defined as a self-report of physician diagnosis or use of glucose-lowering medication.

Kidney Function Estimation

Creatinine measurements were calibrated across study visits to minimize methodological differences and converted to eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[7,8]. End stage renal disease was defined as identification of incident disease due to renal replacement therapy (dialysis, transplant) from the United States Renal Data System (USRDS) during follow-up[9]. For our analysis, participants were assigned an eGFR of 15 ml/min/1.73 m^2 at the onset of end-stage renal disease and then censored, meaning subsequent visit-based eGFR values were not included.

Covariate Assessment

Age, sex, race, history of coronary heart disease, smoking status, annual family income, education status, and use of hypertension and diabetes medications were self-reported[10]. Systolic blood pressure was measured three times using a random zero sphygmomanometer with the participant in the resting state. The second and third measurements were then averaged to obtain one value[11]. Height and weight were measured with standard protocols and the measurements were used to calculate body mass index (weight (kg)/height $(m)^2$)[10].

APOL1 risk status, Hemoglobin A1c (HbA1c), and 1,5-anhydroglucitol were examined among those with diagnosed diabetes. *APOL1* risk status, which has also been

demonstrated to be associated with chronic kidney disease progression[12,13], was assessed in African Americans who provided consent for DNA testing at Visit 1 per methods described previously[13]. We imputed *APOL1* risk status as low-risk for white participants, and characterized black participants as *APOL1*-low risk or *APOL1*-high risk based on the number of risk alleles. HbA1c, a marker of glycemic control and diabetes severity among those with diabetes, was measured in Visit 2 whole blood samples using the Tosoh A1c 2.2 and Tosoh G7 (Tosoh Bioscience)[14], methods certified by the National Glycohemoglobin Standardization Program and aligned to the Diabetes Control and Complications Trial. 1,5-anhydroglucitol (GlycoMark assay), a novel biomarker that reflects hyperglycemic excursions and may be associated with kidney disease progression[15], was measured in serum samples using the Roche Modular P800 Chemistry Analyzer (Roche Diagnostics Corporation). For additional detail on study design and timing of measurements see **Figure B-1**.

Statistical analysis

We categorized people into groups of no diabetes, undiagnosed diabetes, and diagnosed diabetes at baseline (Visit 1), and compared baseline clinical characteristics using ANOVA for continuous variables and Pearson's chi-squared tests for categorical variables. We generated a scatterplot of eGFR and age across visits by diabetes status at baseline, using locally weighted scatterplot smoothing to find a curve of best fit for each diabetes group. To estimate individual eGFR slopes over time, we used linear mixed effects models with random intercepts and random slopes. These models were fit on diabetes status at baseline as a nominal variable to adjust the baseline level of eGFR and included an interaction term between diabetes status at baseline and time to estimate

annual decline in eGFR by diabetes categories. Linear mixed models were run unadjusted and adjusted, with the latter model including the following diabetes and kidney-disease related risk factors: age, sex, race-center, body mass index, systolic blood pressure, hypertension medication use, HDL, prevalent coronary heart disease, annual family income, education status, and smoking status, as well as each variable interacted with time. Continuous covariates were centered at the analytic population mean. We tested model assumptions and considered different covariance structures, comparing nested models using Akaike's Information Criteria. We identified the unstructured covariance model as the most optimal and conservative approach. From the mixed models, we described the overall mean annual decline by diabetes status at baseline, and used the random effects to estimate best linear unbiased predictions to describe the distributions of yearly slopes in eGFR by diabetes status at baseline and displayed them using kernel density plots.

Because of substantial variation in annual eGFR slope among people with diagnosed diabetes, we sought to identify risk factors that were associated with faster decline. Among those with diagnosed diabetes, we compared unadjusted and adjusted mean annual decline in eGFR by race-*APOL1* risk status (white, black- *APOL1* low risk, black- *APOL1* high risk), systolic blood pressure (<140 mmHg, ≥140 mmHg), smoking status (never, former, current), prevalent coronary heart disease (no prevalent coronary heart disease, prevalent coronary heart disease), diabetes medication use (no medication use, oral medication use only [sulfonylureas], and any insulin use), HbA1c (<7%, ≥7 & <9%, ≥9%), and 1,5-anhydroglucitol (≥10 μg/mL, <10 μg/mL). Because some of these variables were only available at Visit 2, we required that participants included in this

subgroup analysis attend both Visit 1 and Visit 2 and not be missing information on *APOL1* or the variables assessed at Visit 2 to ensure a consistent sample size. In addition to diabetes and kidney-disease related risk factors in the adjusted model, we also included diabetes medication use and HbA1c to account for diabetes severity in these analyses.

Next, to enable assessment of potential hyperfiltration, we used a linear spline model to allow the slope to change for each of the diabetes categories between the first 3 years of follow-up (Visit 1 to Visit 2) and the subsequent time period (Visit 2 to Visit 5). We reported the unadjusted and adjusted distributions of annual eGFR slopes by diabetes status (assessed at baseline) from Visit 1 to Visit 2 and Visit 2 to Visit 5.

To test the robustness of our results, we conducted a sensitivity analysis where we did not assign eGFR values of 15 ml/min/1.73 m^2 in those who developed end stage renal disease. All analyses were conducted in Stata 13 (StataCorp, College Station, TX).

Results

Study Population Characteristics

There were 15,517 participants included in the analysis: 13,698 (88%) without diabetes, 634 (4%) with undiagnosed diabetes, and 1,185 (8%) with diagnosed diabetes at baseline. There were 47,695 total eGFR measurements, three or more measurements per person among 76% of participants (78% among no diabetes, 67% among undiagnosed diabetes, 58% among diagnosed diabetes), and 375 cases of end-stage renal disease during follow-up (188 among no diabetes, 38 among undiagnosed diabetes, 149 among diagnosed diabetes).

At baseline, participants with undiagnosed and diagnosed diabetes were older, more likely to be black, more likely to have hypertension and coronary heart disease, and

had higher mean body mass index and lower mean HDL, compared to those without diabetes (**Table 1**). Income and education levels were also lower among those with undiagnosed and diagnosed diabetes compared to those without diabetes.

Decline in eGFR by Diabetes Status

Overall, there was a nearly linear association between eGFR and age over time, regardless of diabetes status (**Figure 1**). The crude mean annual decline in eGFR was slowest among those without diabetes at baseline (decline of -1.6 ml/min/1.73 m^2 per year [95% CI, -1.6, -1.5]), faster among those with undiagnosed diabetes at baseline compared to those without diabetes (decline of -2.1 ml/min/1.73 m^2 per year [95% CI, -2.2, -2.0]; difference of -0.6 ml/min/1.73 m^2 per year [95% CI, -0.7, -0.4]), and nearly twice as rapid among those with diagnosed diabetes compared to those without diabetes (decline of -2.9 ml/min/1.73 m^2 per year [95% CI, -3.0, -2.8]; difference of -1.3 ml/min/1.73 m^2 per year [95% CI, -1.4, -1.2]). Adjustment for diabetes and kidney disease-related risk factors attenuated the results slightly, but those with undiagnosed and diagnosed diabetes still had statistically significantly steeper declines than those without diabetes (decline among those without diabetes: -1.4 ml/min/1.73 m^2 per year [95% CI -1.5, -1.4]; decline among those with undiagnosed diabetes: -1.8 ml/min/1.73 m^2 per year [95% CI -2.0, -1.7], difference vs. no diabetes of -0.4 ml/min/1.73 m^2 per year [95% CI, -0.5, -0.3, $p<0.001$]; decline among those with diagnosed diabetes: -2.5 ml/min/1.73 m^2 per year [95% CI -2.6, -2.4], difference vs. no diabetes of -1.1 ml/min/1.73 m^2 per year [95% CI, -1.2, -1.0, $p<0.001$]).

The decline in eGFR per year varied greatly across individuals, particularly among those with diabetes at baseline (**Figure 2**). Crude yearly individual predicted

slopes ranged from (10^{th} to 90^{th} percentile) -2.3 to -1.0 ml/min/1.73 m^2 per year among those without diabetes (median: -1.6 ml/min/1.73 m^2 per year); this range was from -3.1 to -1.4 ml/min/1.73 m^2 per year among those with undiagnosed diabetes (median: -2.1 ml/min/1.73 m^2 per year); and from -4.1 to -2.0 ml/min/1.73 m^2 per year among those with diagnosed diabetes (median: -2.9 ml/min/1.73 m^2 per year). While adjustment for risk factors related to diabetes and kidney disease reduced some of the variation between diabetes categories, the differences in eGFR decline were still statistically significant.

Factors Associated with eGFR Decline Among Diagnosed Diabetes

Among participants with diagnosed diabetes at baseline, those who were black, who had systolic blood pressure ≥140 mmHg, who used diabetes medications, had a HbA1c ≥7%, or had 1,5-anhydroglucitol <10 μg/mL were at risk for steeper annual declines than their counterparts (**Table 2**). Smoking status and prevalent coronary heart disease were not associated with significantly steeper eGFR decline in unadjusted analyses. Adjustment for diabetes- and kidney disease-related risk factors and diabetes medication use and HbA1c (used as proxies for diabetes severity), attenuated the differences in decline for all subgroups with the exception of smoking status, leaving black race along with *APOL1* susceptible genotype, systolic blood pressure ≥140 mmHg, current smoking, insulin use, and HbA1c ≥9% as the risk factors indicative of steeper decline.

eGFR Trajectories by Time Period

When the effect of diabetes on eGFR decline was assessed in two different time periods, we saw potential evidence of hyperfiltration. From Visit 1 to Visit 2, the distribution of adjusted decline in eGFR among those with undiagnosed diabetes at

baseline was less negative than those without diabetes, suggesting that they did not experience as much decline over the 3-year interval (**Figure 3**). Similarly, the adjusted mean annual decline in eGFR was largest among those with diagnosed diabetes, followed by those without diabetes, and then by those with undiagnosed diabetes at baseline (-2.5 ml/min/1.73 m^2 per year [95% CI, -2.8, -2.1]; -1.7 ml/min/1.73 m^2 [95% CI, -1.9, -1.4]; and -1.3 ml/min/1.73 m^2 per year [95% CI, -1.7, -0.8], respectively). This resulted in a difference in slope over the first three years comparing undiagnosed to no diabetes at baseline of 0.4 ml/min/1.73 m^2 per year (95% CI, 0.1, 0.8). The unadjusted distribution of slopes and mean decline and followed a similar pattern. Additionally, those with undiagnosed diabetes showed suggestion of a higher eGFR at baseline than those without diabetes at baseline in the unadjusted model (0.7 ml/min/1.73 m^2 [95% CI -0.6, 2.0]), which was statistically significantly higher after adjustment (2.3 ml/min/1.73 m^2 [95% CI 1.1, 3.4]).

Over the remainder of follow-up, from Visit 2 to Visit 5, we observed that the distributions of unadjusted and adjusted slopes among those with undiagnosed diabetes at baseline were more negative than those without diabetes at baseline (**Figure B-2**).

Sensitivity analyses without imputation of eGFR for those who developed end stage renal disease attenuated the values of the mean annual declines in eGFR, but the significant differences between diabetes categories remained (**Table B-1**).

Discussion

In this prospective, community-based cohort followed for over 26 years, we observed that diabetes is an important risk factor for kidney function decline. Persons with undiagnosed diabetes at baseline were also at higher risk of eGFR decline;

interestingly, this followed a period of relatively little average eGFR decline, which may reflect early hyperfiltration. Large individual variation in eGFR trajectories was observed, particularly among persons with diabetes, with race, systolic blood pressure, and glycemia explaining some of the risk differences. Given the well-established evidence that glycemic control prevents or slows microvascular damage, our findings reinforce the need for early diagnosis of diabetes and glycemic control following diagnosis[16–18]. Our results also suggest racial disparities persist over and above measured genetic and traditional risk factors.

Few other community-based studies have evaluated differences in kidney function decline by diabetes status over a long period through mid- and late-life. One study of 10,184 Canadians aged 66 years or older with creatinine measured during outpatient visits showed results largely consistent our findings but with much shorter follow-up (median of 2 years)[19].

Other studies of eGFR change in a general population have found smaller declines than our results[20,21]. A study conducted in Japanese participants aged 40 to 79 years found a decline of only -0.4 ml/min/1.73 m^2 per year over the course of two assessments 10 years apart (compared to our estimate among those without diabetes: -1.6 ml/min/1.73 m^2 per year). This is particularly interesting, as Japan is known to have a higher prevalence of chronic kidney disease and end-stage renal disease than the U.S.[20]. However, this study evaluated participants over a shorter time frame and required attendance at both assessments, which may decreased the likelihood of capturing severe cases and resulted in underestimation of decline.

The Baltimore Longitudinal Study of Aging also assessed kidney function over time in a general population of 446 men, ranging in age from 22 to 97 years at baseline, each with up to 14 measurements of creatinine clearance assessed between 1958 and 1981[21]. They also found a smaller decline than we did (-0.8 ml/min per year), although this study also had notable differences. Their main analysis excluded participants with hypertension and history of renal disease or urinary tract infection, and those treated with diuretics and/or anti-hypertensive medications. Without applying those exclusions, their overall estimate was -1.1 ml/min per year, which better reflects a community-based population and our results. The study also took place prior to ARIC, and risk factor and treatment patterns may have differed due to secular trends. In addition, they used creatinine clearance instead of eGFR as a measure of kidney function, and while this may not affect computation of change, creatinine clearance estimates are known to be higher than GFR[22].

In our evaluation of risk factors that might explain the variation in decline seen among those with diagnosed diabetes, we observed that black race, systolic blood pressure ≥140 mmHg, insulin use, and HbA1c ≥9% were particularly important. Although the *APOL1* high-risk genotype is a known risk factor for eGFR decline, African-Americans with low-risk *APOL1* status continued to be at higher risk than whites even after adjustment for traditional risk factors, diabetes medication use, and HbA1c. This suggests there could be differences over time by risk factors, diabetes severity, access to health care, quality of health care, or health care utilization not accounted for in our analysis.

Our results are relevant to the design and conduct of clinical trials. Hard clinical outcomes like end-stage renal disease are relatively rare and a 30-40% decline in eGFR is now accepted as a surrogate endpoint for chronic kidney disease progression[4]. We provide data on patient subgroups that may experience accelerated trajectories of kidney function decline, which has implications for estimating sample size and ensuring adequate power in future clinical trials. Our results also suggest that endpoints of eGFR decline might not be appropriate for patients with new onset diabetes, where declines may actually be slower than among persons without diabetes.

Slower eGFR decline among those with undiagnosed diabetes, who are likely early in the course of diabetes is consistent with the hypothesis of hyperfiltration. Similar to other studies, we found that persons with undiagnosed diabetes had higher GFR at the outset, but this was a transient phenomenon as they ultimately experienced larger declines in kidney function than those without diabetes over the course of follow-up[23–25]. Whether hyperfiltration is a universal aspect of early disease and, if not, whether it portends worse long-term outcomes is uncertain. Existing studies investigating hyperfiltration as a precursor to adverse kidney outcomes are inconsistent[24,26,27] and often confounded by diabetes severity factors like duration[27]. We extended this literature by separating undiagnosed and diagnosed diabetes to help address that confounding.

Our analysis has certain limitations. Detection of possible hyperfiltration was limited to two measurements of eGFR per person over a three-year time interval, and up to three measurements in the subsequent 23 years. Undiagnosed diabetes at Visit 1 was defined solely by glucose, which may have led to some misclassification. A single measurement of fasting glucose is prone to measurement error, given that only 76% of

those with diabetes by a single fasting glucose are confirmed by a second measurement. This suggests we could have overestimated the prevalence of undiagnosed diabetes, although this bias would be conservative[28]. There were also changes in clinical definitions of diabetes during the study period. At the time of Visit 1 (1987-1989), a higher threshold of glucose was recommended for the diagnosis of diabetes (140 mg/dL). We employed a more conservative definition (≥126 mg/dL) for consistency with current clinical guidelines[29]. Additionally, while we were able to use undiagnosed diabetes to likely capture those early in the course of disease, we did not have information on diabetes duration at baseline among those with undiagnosed or diagnosed diabetes. Finally, albuminuria, itself a strong predictor of eGFR decline, was not assessed in ARIC until Visit 4.

Study strengths include the racially diverse community-based cohort of middle-aged adults in the U.S. in the late 1980s followed through the early 2010s. Changes in kidney function were captured prior to the approval of new diabetes medications with kidney-related effects, such as sodium-glucose cotransporter (SGLT)-2 inhibitors, which might confound results. We also had complete follow-up for end stage renal disease from the linkage of ARIC to the USRDS surveillance system, allowing us to account for those who develop end-stage renal disease, even if they did not return to a study visit.

In conclusion, we found that diabetes was associated with much steeper kidney function decline in a community-based population followed over 26 years. We quantified the annual expected decline in eGFR among those without diabetes, with undiagnosed diabetes, and with diagnosed diabetes, which may be useful to inform future monitoring

and clinical trials. Our results reinforce the importance of glycemic and risk factor control in the prevention of chronic kidney disease and end stage renal disease.

Table 1. Baseline* characteristics of participants by diabetes status at Visit 1 (1987-89)

	No diabetes n=13,698	Undiagnosed diabetes n=634	Diagnosed diabetes n=1,185	p-value†
Age (years)	54.5 (5.7)	56.0 (5.7)	56.4 (5.7)	<0.001
Female, %	55.2	48.4	57.6	<0.001
Race-center, %				
Forsyth County, NC – White	23.5	16.7	16.0	<0.001
Forsyth County, NC – Black	2.9	4.4	4.8	
Jackson, MS – Black	21.1	31.1	41.7	
Minneapolis, MN – White	26.8	23.2	12.7	
Washington County, MD – White	25.7	24.6	24.7	
eGFR (mL/min/1.73 m^2)	102.6 (14.7)	103.3 (17.5)	102.3 (20.9)	0.42
eGFR <60 mL/min/1.73 m^2, %	0.9	1.4	4.1	<0.001
Systolic blood pressure (mmHg)	120.1 (18.3)	130.4 (19.6)	129.1 (21.3)	<0.001
Hypertension, %	31.4	59.8	60.1	<0.001
Body mass index (kg/m^2)	27.2 (5.1)	31.2 (5.7)	31.0 (6.0)	<0.001
HDL (mg/dL)	52.5 (17.2)	43.6 (13.5)	45.2 (15.4)	<0.001
Prevalent coronary heart disease, %	4.2	6.6	12.6	<0.001
Smoking status, %				
Never smoker	41.2	42.7	44.9	0.018
Former smoker	32.3	34.9	31.1	
Current smoker	26.5	22.4	24.0	
Annual family income less than $25,000, %	35.2	49.2	61.3	<0.001
Educational status, %				
Less than high school	8.4	12.8	19.7	<0.001
High school	46.1	49.1	50.5	
Vocational school	8.6	8.2	6.8	
College	26.5	21.8	16.9	
Graduate/professional school	10.4	8.2	6.1	

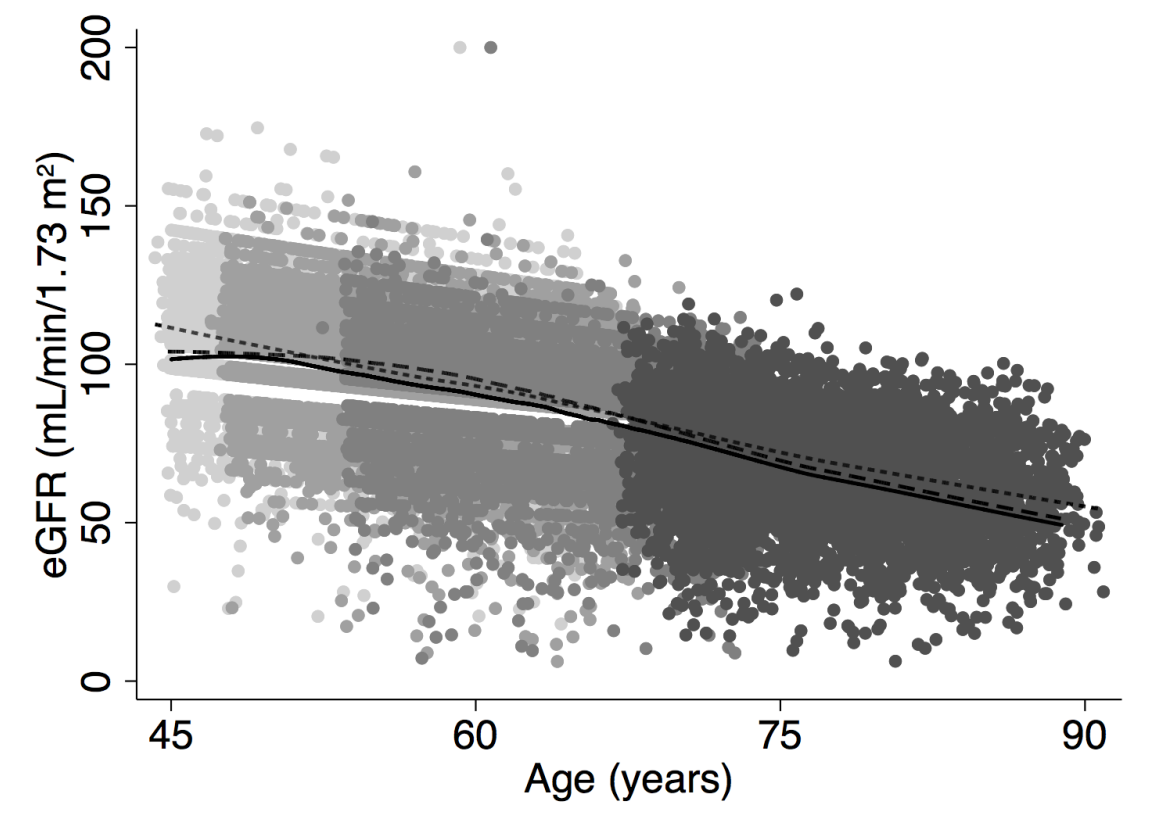
Data are means (SD) unless otherwise noted

* Baseline variables with missingness (variable, n): systolic blood pressure, 7; hypertension, 75; body mass index, 13; HDL, 109; prevalent coronary heart disease, 319; smoking status, 14; annual family income, 898; and educational status, 25

† *p*-value for global test: ANOVA for continuous variables and Pearson's chi-squared tests for categorical variables

Abbreviations: *eGFR* estimated glomerular filtration rate; *HDL* high-density lipoprotein

Figure 1. Scatterplot of eGFR and age according to visit with lowess smoothers by diabetes status at baseline



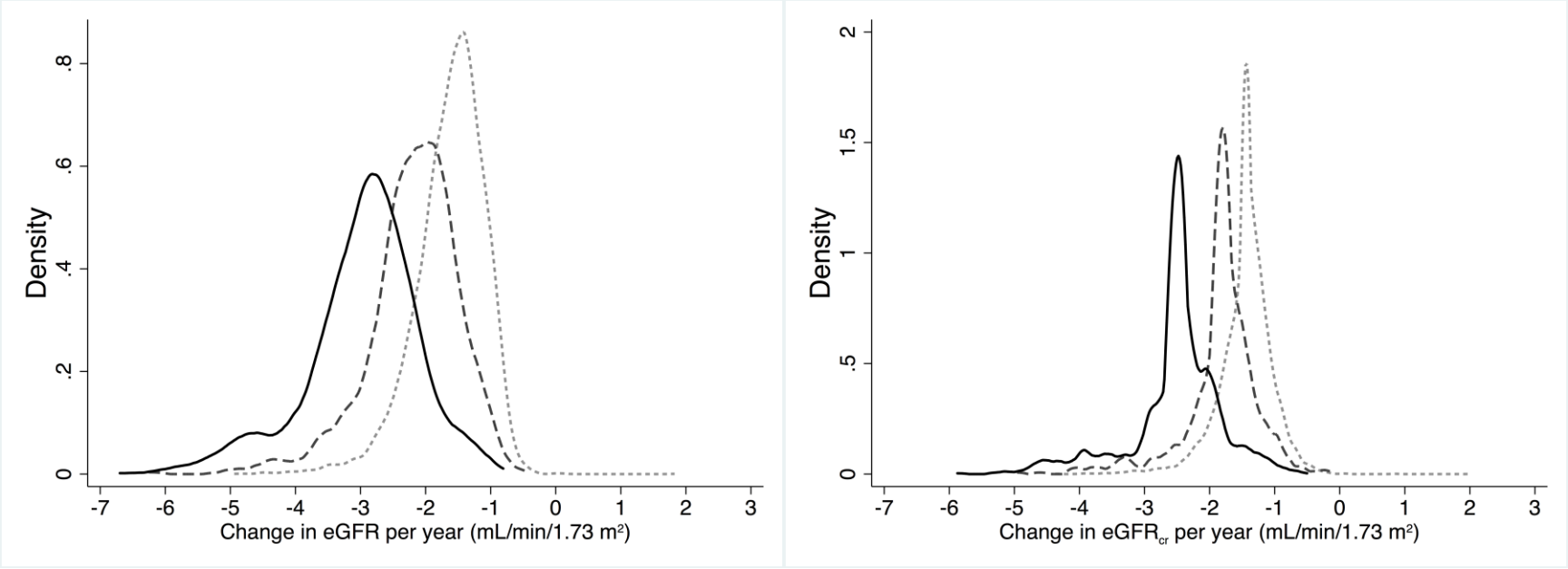
Abbreviations: *eGFR* estimated glomerular filtration rate

Legend

Visit 1 Visit 2 Visit 4 Visit 5; No diabetes Undiagnosed diabetes Diagnosed diabetes

Figure 2. Distribution of annual unadjusted and adjusted eGFR slopes from best linear unbiased predictions, by diabetes status

Unadjusted **Adjusted**



	Percentile and corresponding change in eGFR per year (mL/min/1.73m^2)									
	Unadjusted					Adjusted*				
	10th	25th	50th	75th	90th	10th	25th	50th	75th	90th
No diabetes	-2.3	-1.9	-1.6	-1.3	-1.0	-1.9	-1.6	-1.4	-1.2	-1.0
Undiagnosed diabetes	-3.1	-2.5	-2.1	-1.7	-1.4	-2.4	-2.0	-1.8	-1.5	-1.3
Diagnosed diabetes	-4.1	-3.4	-2.9	-2.4	-2.0	-3.5	-2.7	-2.5	-2.2	-1.8

* Adjusted for the following characteristics at baseline and their interactions with time, continuous variables centered at their means: age (ref=54.67 years), sex (ref=male), race-center (ref=Forsyth County-White; Forsyth County-Black, Jackson-Black, Minneapolis-White, Washington County-White), systolic blood pressure (ref=121.22), hypertension medication use (ref=no; yes), body mass index (ref=27.68), HDL (ref=51.60), prevalent coronary heart disease (ref=no; yes), smoking status (ref=never; former, current), annual family income (ref: <$25,000; ≥$25,000), and educational status (ref: high school; less than high school, vocational school, college, graduate/professional school)

Abbreviations: *eGFR* estimated glomerular filtration rate

Legend: ·····No diabetes – – – –Undiagnosed diabetes ——— Diagnosed diabetes

Table 2. Unadjusted and adjusted differences in mean annual change in eGFR among those with diagnosed diabetes who attended Visits 1 & 2, by subgroups of interest, n=838

Subgroup	n	Unadjusted difference (95%CI) from reference, ml/min/1.73m^2	*p*-value for difference	Adjusted* difference (95%CI) from reference, ml/min/1.73m^2	*p*-value for difference
Race and APOL1† (Visit 1)					
White	495	0 (REF)		0 (REF)	
Black – APOL1 Low Risk	290	-1.3 (-1.7, -0.9)	<0.001	-0.7 (-1.2, -0.3)	0.001
Black – APOL1 High Risk	53	-1.7 (-2.5, -1.0)	<0.001	-1.3 (-2.1, -0.6)	0.001
Systolic blood pressure‡ (Visit 1)					
< 140 mmHg	643	0 (REF)		0 (REF)	
≥ 140 mmHg	195	-1.3 (-1.7, -0.8)	<0.001	-1.0 (-1.4, -0.5)	<0.001
Smoking status§ (Visit 1)					
Never Smoker	400	0 (REF)		0 (REF)	
Former Smoker	258	0.1 (-0.4, 0.5)	0.808	-0.2 (-0.7, 0.2)	0.271
Current Smoker	180	-0.3 (-0.8, 0.2)	0.224	-0.6 (-1.1, -0.1)	0.018
Prevalent coronary heart disease‖ (Visit 1)					
No prevalent coronary heart disease	743	0 (REF)		0 (REF)	
Prevalent coronary heart disease	95	-0.6 (-1.3, 0.0)	0.068	-0.6 (-1.2, 0.1)	0.080
Diabetes medication use¶ (Visit 1)					
No medication use	279	0 (REF)		0 (REF)	
Oral medication use only	319	-0.7 (-1.1, -0.3)	0.002	-0.3 (-0.7, 0.2)	0.270
Any insulin use	240	-1.8 (-2.2, -1.3)	<0.001	-1.1 (-1.6, -0.6)	<0.001

* Adjusted for the following characteristics at baseline and their interactions with time, continuous variables centered at their means: age (ref=56.09 years), sex (ref=male), race-center (ref=Forsyth County-White; Forsyth County-Black, Jackson-Black, Minneapolis-White, Washington County-White), systolic blood pressure (ref=128.04), hypertension medication use (ref=no; yes), body mass index (ref=30.87), HDL (ref=45.08), prevalent coronary heart disease (ref=no; yes), smoking status (ref=never; former, current), annual family income (ref: <$25,000; ≥$25,000), and educational status (ref: high school; less than high school, vocational school, college, graduate/professional school)**,** diabetes medication use (ref=no medication use; oral medication use only, any insulin use), and HbA1c (ref=8.49)

Adjusted for all covariates with the exception of: † race-center; ‡ systolic blood pressure; § smoking status; ‖ prevalent coronary heart disease; ¶ diabetes medication use; # HbA1c

** Adjusted difference from REF when 1,5-anhydroglucitol is adjusted for all covariates except HbA1c: -0.4 ml/min/1.73m^2 (95% CI, -0.8, 0.0), p=0.060

Abbreviations: *eGFR* estimated glomerular filtration rate; *HbA1c* hemoglobin A1c

Table 2., continued

Subgroup	n	Unadjusted difference (95%CI) from reference, ml/min/1.73m^2	*p*-value for difference	Adjusted* difference (95%CI) from reference, ml/min/1.73m^2	*p*-value for difference
HbA1c# (Visit 2)					
< 7%	250	0 (REF)		0 (REF)	
≥ 7 & < 9%	270	-0.6 (-1.0, -0.1)	0.011	-0.1 (-0.6, 0.4)	0.623
≥ 9%	318	-1.5 (-1.9, -1.0)	<0.001	-0.7 (-1.2, -0.2)	0.004
1,5-anhydroglucitol** (Visit 2)					
≥ 10 µg/mL	238	0 (REF)		0 (REF)	
< 10 µg/mL	600	-0.9 (-1.3, -0.5)	<0.001	0.1 (-0.4, 0.6)	0.717

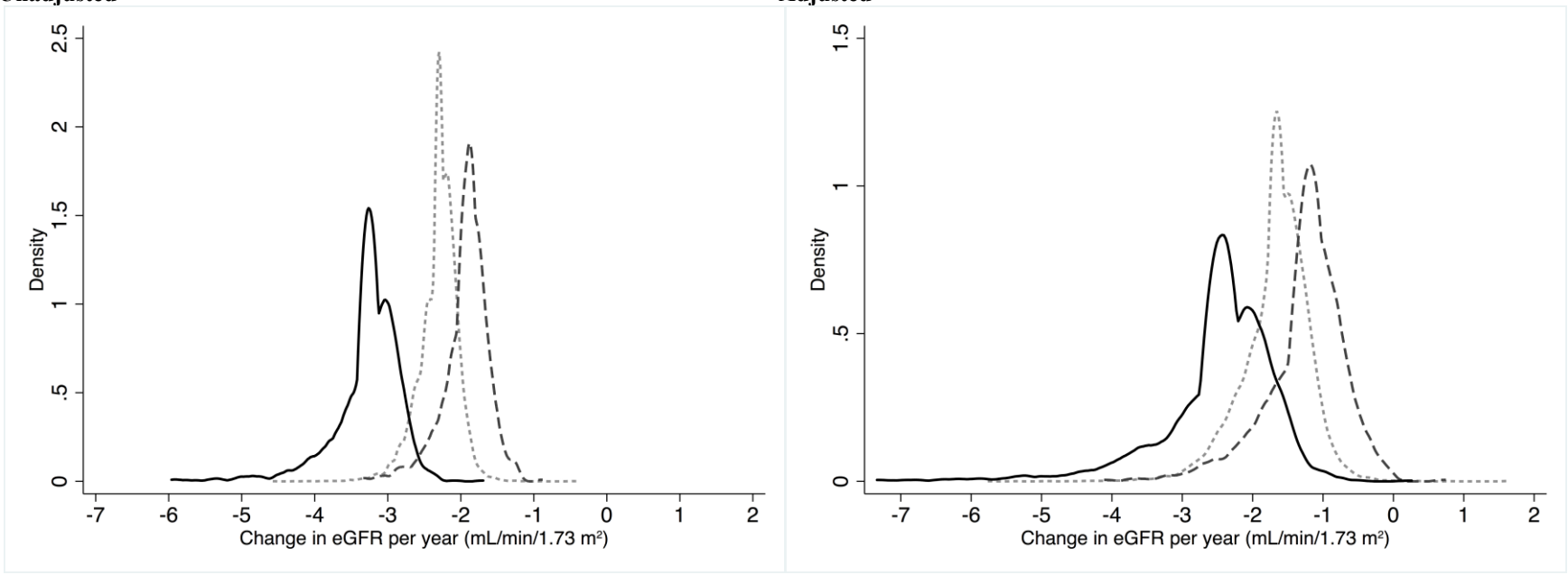
* Adjusted for the following characteristics at baseline and their interactions with time, continuous variables centered at their means: age (ref=56.09 years), sex (ref=male), race-center (ref=Forsyth County-White; Forsyth County-Black, Jackson-Black, Minneapolis-White, Washington County-White), systolic blood pressure (ref=128.04), hypertension medication use (ref=no; yes), body mass index (ref=30.87), HDL (ref=45.08), prevalent coronary heart disease (ref=no; yes), smoking status (ref=never; former, current), annual family income (ref: <$25,000; ≥$25,000), and educational status (ref: high school; less than high school, vocational school, college, graduate/professional school)**,** diabetes medication use (ref=no medication use; oral medication use only, any insulin use), and HbA1c (ref=8.49)

Adjusted for all covariates with the exception of: † race-center; ‡ systolic blood pressure; § smoking status; || prevalent coronary heart disease; ¶ diabetes medication use; # HbA1c

** Adjusted difference from REF when 1,5-anhydroglucitol is adjusted for all covariates except HbA1c: -0.4 ml/min/1.73m^2 (95% CI, -0.8, 0.0), *p*=0.060

Abbreviations: *eGFR* estimated glomerular filtration rate; *HbA1c* hemoglobin A1c

Figure 3. Distribution of annual unadjusted and adjusted eGFR slopes from Visit 1 to Visit 2 from best linear unbiased predictions, by diabetes status



	Percentile and corresponding change in eGFR per year (mL/min/1.73m2)									
	Unadjusted					Adjusted*				
	10th	25th	50th	75th	90th	10th	25th	50th	75th	90th
No diabetes	-2.6	-2.4	-2.3	-2.1	-2.0	-2.3	-1.9	-1.6	-1.4	-1.2
Undiagnosed diabetes	-2.3	-2.1	-1.9	-1.7	-1.6	-2.0	-1.5	-1.2	-0.9	-0.7
Diagnosed diabetes	-3.8	-3.4	-3.3	-3.0	-2.8	-3.5	-2.7	-2.4	-2.0	-1.7

* Adjusted for the following characteristics at baseline and their interactions with time, continuous variables centered at their means: age (ref=54.67 years), sex (ref=male), race-center (ref=Forsyth County-White; Forsyth County-Black, Jackson-Black, Minneapolis-White, Washington County-White), systolic blood pressure (ref=121.22), hypertension medication use (ref=no; yes), body mass index (ref=27.68), HDL (ref=51.60), prevalent coronary heart disease (ref=no; yes), smoking status (ref=never; former, current), annual family income (ref: <$25,000; ≥$25,000), and educational status (ref: high school; less than high school, vocational school, college, graduate/professional school); Abbreviations: *eGFR* estimated glomerular filtration rate

Legend: ·····No diabetes – – – –Undiagnosed diabetes ——— Diagnosed diabetes

Chapter 2. Comparative prognostic performance of definitions of prediabetes: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study

Lancet Diabetes Endocrinology 2017;5(1):p.34-42

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Abstract

Background. No consensus on definitions of prediabetes exists among international organisations. Analysis of associations with different definitions and clinical complications can inform the comparative value of different prediabetes definitions. We compared the risk of future outcomes across different prediabetes definitions based on fasting glucose concentration, HbA1c, and 2 h glucose concentration during over two decades of follow-up in the community-based Atherosclerosis Risk in Communities (ARIC) study. We aimed to analyse the associations of definitions with outcomes to provide a comparison of different definitions.

Methods. We did a prospective cohort study of participants in the ARIC study who did not have diagnosed diabetes and who attended visit 2 (1990–92; n=10844) and who attended visit 4 (1996–98; n=7194). ARIC participants were enrolled from four communities across the USA. Fasting glucose concentration and HbA1c were measured at visit 2 and fasting glucose concentration and 2 h glucose concentration were measured at visit 4. We compared prediabetes definitions based on fasting glucose concentration (American Diabetes Association [ADA] fasting glucose concentration cutoff 5.6–6.9

mmol/L and WHO fasting glucose concentration cutoff 6.1–6.9 mmol/L), HbA1c (ADA HbA1c cutoff 5.7–6.4% [39–46 mmol/mol] and International Expert Committee [IEC] HbA1c cutoff 6.0–6.4% [42–46 mmol/mol]), and 2 h glucose concentration (ADA and WHO 2 h glucose concentration cutoff 7.8–11.0 mmol/L).

Findings. Prediabetes defined using the ADA fasting glucose concentration cutoff (prevalence 4112 [38%] of 10 844 people; 95% CI 37.0–38.8) was the most sensitive for major clinical outcomes, whereas using the ADA HbA1c cutoff (2027 [19%] of 10884 people; 18.0–19.4) and IEC HbA1c cutoff (970 [9%] of 10844 people; 8.4–9.5), and the WHO fasting glucose concentration cutoff (1213 [11%] of 10844 people; 10.6–11.8) were more specific. After demographic adjustment, HbA1c -based definitions of prediabetes had higher hazard ratios and better risk discrimination for chronic kidney disease, cardiovascular disease, peripheral arterial disease, and all-cause mortality than did fasting glucose concentration-based definitions (all $p<0.05$). The C-statistic for incident chronic kidney disease was 0.636 for ADA fasting glucose concentration clinical categories and 0.640 for ADA HbA1c clinical categories (difference –0.005, 95% CI –0.008 to –0.001). The C-statistics were 0.662 for ADA fasting glucose clinical concentration categories and 0.672 for ADA HbA1c clinical categories for atherosclerotic cardiovascular disease, 0.701 for ADA fasting glucose concentration clinical categories and 0.722 for ADA HbA1c clinical categories for peripheral arterial disease, and 0.683 for ADA fasting glucose concentration clinical categories and 0.688 for ADA HbA1c clinical categories for all-cause mortality. Prediabetes defined using the ADA HbA1c cutoff showed a significant overall improvement in the net reclassification index for cardiovascular outcomes and death compared with prediabetes defined with glucose-

based definitions. ADA fasting glucose concentration clinical categories, WHO fasting glucose concentration clinical categories, and ADA and WHO 2 h glucose concentrations clinical categories were not significantly different in terms of risk discrimination for chronic kidney disease, cardiovascular outcomes, or mortality outcomes.

Interpretation. Our results suggest that prediabetes definitions using HbA1c were more specific and provided modest improvements in risk discrimination for clinical complications. The definition of prediabetes using the ADA fasting glucose concentration cutoff was more sensitive overall.

Funding US National Institutes of Health.

Introduction

Prediabetes is a pressing clinical and public health problem that affects approximately 12–30% of US adults aged 18 years and older, depending on the definition used.[1] International organisations largely agree on the clinical cutoff points for diagnosis of diabetes and, in 2010, HbA1c ≥6.5% (≥48 mmol/mol) was adopted for diagnosis of diabetes by many international groups, in part based on the association of HbA1c with retinopathy.[2–5] By contrast, the category of prediabetes does not have a uniform definition. The American Diabetes Association (ADA) recommends using the following criteria to identify people with prediabetes: fasting glucose con centration between 5.6 and 6.9 mmol/L (100–125 mg/dL; impaired fasting glucose), HbA1c of 5.7–6.4% (39–46 mmol/mol), or 2 h glucose concentration after a 75 g oral glucose tolerance test of 7.8–11.0 mmol/L (140–199 mg/dL; impaired glucose tolerance).[6] WHO also recommends 2 h glucose of 7.8–11.0 mmol/L to identify impaired glucose tolerance, but recommends a fasting glucose concentration of 6.1–6.9 mmol/L (110–125 mg/dL) to identify impaired

fasting glucose.[2] In 2009, the International Expert Committee (IEC) recommended HbA1c of 6.0–6.4% (42–46 mmol/mol) for the identification of an intermediate risk group, which has been adopted by some organisations.[5] Identification of individuals with pre- diabetes provides an opportunity for intervention through lifestyle modification and pharmacological interventions to prevent progression to diabetes.[6,7] Consensus on definitions of prediabetes could help guide resource allocation and aid public health efforts to identify people at risk of developing diabetes and its complications.

Although the selection of biomarker cutoff points for screening or diagnosis requires a broad range of considerations, associations with clinical outcomes are an important factor.[8] Therefore, the aim of this study was to compare the prognostic performance of the abovementioned definitions of prediabetes in their associations with major clinical complications such as incident diabetes, chronic kidney disease, atherosclerotic cardiovascular disease, peripheral arterial disease, and all-cause mortality. We compared the risk of future outcomes across different definitions of prediabetes by fasting glucose concentration, HbA1c, and 2 h glucose concentration during over two decades of follow-up in the community-based Atherosclerosis Risk in Communities (ARIC) study.

Methods

Study design and participants

This prospective cohort study was based on the ARIC study, which originally enrolled 15792 adults aged 45–64 years from the communities of Jackson, MS; Forsyth County, NC; suburban Minneapolis, MN; and Washington County, MD, USA. We excluded participants with prevalent diabetes, chronic kidney disease, atherosclerotic

cardiovascular disease, or peripheral arterial disease, those who were missing variables of interest, or those who fasted for less than 10 h (see appendix for full details). Detailed methods of the study have been previously published.[9] Briefly, the first examination, including medical, social, and demographic assessment, took place from 1987 to 1989, with three follow-up visits approximately every 3 years, and a fifth visit between 2011 and 2013. Institutional review board approval was acquired at all study sites and written consent was obtained from all participants.

Procedures

We did two main comparisons. First, with visit 2 (1990–92) as baseline, when both fasting glucose concentration and HbA1c were measured. And, second, with visit 4 (1996–98) as baseline, when both fasting glucose concentration and 2 h glucose concentration were measured. Our final sample size included 10 844 participants who attended visit 2 and 7194 participants who attended visit 4 (appendix). Fasting glucose was measured using a hexokinase method in serum at visit 2 and in plasma at visit 4. We formally compared and recalibrated fasting glucose concentrations to ensure equivalence of the measurements over time.[10] HbA1c was measured in stored whole-blood samples from visit 2 by high-performance liquid chromatography using the Tosoh A1c 2.2 Plus and Tosoh G7 methods (Tosoh Bioscience, San Francisco, CA, USA), aligned to those used in the Diabetes Control and Complications Trial.[11] 2 h plasma glucose concentration was measured following a 75 g oral glucose tolerance test administered using a hexokinase method at visit 4.[12] We defined prediabetes using three definitions recognised by the ADA: fasting glucose concentration cutoff 5.6–6.9 mmol/L, HbA1c cutoff 5.7–6.4% (39–46 mmol/mol), and 2 h glucose cutoff 7.8–11.0 mmol/L, along with definitions

recommended by WHO (fasting glucose concentration cutoff 6.1–6.9 mmol/L), and IEC (HbA1c cutoff 6.0–6.4% [42–46 mmol/mol]).

Participants were prospectively followed up and incidents of diabetes, chronic kidney disease, atherosclerotic cardiovascular disease (coronary heart disease and ischaemic stroke), peripheral arterial disease, and all-cause mortality were recorded until end of follow-up in 2013 (loss to follow-up was also recorded). Incident diabetes was defined by self-report of a physician diagnosis of diabetes or use of glucose-lowering medication reported during a study visit or annual telephone call.[13,14] Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min per 1.73 m² measured at a study visit and a reduction in eGFR of at least 25% from the baseline visit to the follow-up visit, or chronic kidney disease-related hospital admission or death by continuous active surveillance, or an end-stage renal disease event identified by the US Renal Data System registry.[15] Incident atherosclerotic cardiovascular disease events were adjudicated and included any coronary heart disease hospital admission or death, or ischaemic stroke hospital admission or death, and were obtained by continuous active surveillance. Peripheral arterial disease events were identified from hospital admission records (International Classification of Diseases 9 discharge codes) for peripheral arterial disease (440.2, 440.3, 440.4) or leg revascularisation (38.18, 39.25, 39.29, 39.50). All-cause mortality was ascertained from hospital and National Death Index records. BMI, waist-to-hip ratio, blood pressure, lipid concentrations, and eGFR (calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration Equation)[16] were measured following standard protocols.[17–19] Age, sex, race centre (white, Minneapolis; black, Jackson; white, Washington County; black,

Forsyth County; white, Forsyth County; as defined in the ARIC study design), education level, smoking status, alcohol use, parental history of diabetes, and use of lipid-lowering medications were reported at study visits. Hypertension was defined as an elevated systolic (≥140 mm Hg) or diastolic (≥90 mm Hg) blood pressure from the mean of two measurements taken at a study visit or the use of blood-pressure-lowering medications.

Statistical analysis

We compared baseline characteristics of the study participants at the relevant visit across clinical categories (normoglycaemia, prediabetes, and undiagnosed diabetes) for the different definitions of prediabetes. We calculated sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio of each prediabetes definition using 10 year Kaplan-Meier estimates comparing people with prediabetes to those with normoglycaemia against people with and without the events of interest. Cox proportional hazards models were used to estimate adjusted hazard ratios of incident events associated with the different clinical categories, with normoglycaemia as the reference group. Demographic-adjusted models included age, sex, and race centre. Fully adjusted models included all variables in demographic-adjusted models plus education level, BMI, waist-to-hip ratio, total cholesterol concentration, HDL cholesterol concentration, triglyceride concentrations, eGFR, hypertension, smoking status, alcohol use, lipid-lowering medication use, and family history of diabetes. We used Harrell's C-statistic to compare discrimination of models with the different clinical categories with respect to future outcomes and obtained 95% CIs with a jackknife approach.[20] We calculated the continuous net reclassification index (cNRI) for 10 year risk of each outcome for the different clinical categories, using

prediabetes defined using ADA fasting glucose concentration cutoffs as the reference. We did sensitivity analyses stratifying by race and sex and after excluding people with undiagnosed diabetes.[21]

As an ancillary analysis, we replicated our study using data from the Third National Health and Nutrition Examination Survey (NHANES III), a nationally representative sample of the US population, to assess the generalisability of our results (appendix). Only prospective information on fatal cardiovascular disease and all-cause mortality was available in NHANES. All analyses were done using Stata/SE (version 13).

Role of the funding source

The funder of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to the data and the corresponding author had final responsibility to submit for publication.

Results

In comparison with people with prediabetes defined using ADA fasting glucose concentration cutoffs at visit 2, use of ADA HbA1c cutoffs to define prediabetes was more likely to identify people who were women, black, current smokers, had hypertension, and who had less high-school education; it was less likely to identify current drinkers (**Table 1**). In comparison with people defined using ADA fasting glucose concentration cutoffs at visit 4, use of ADA and WHO 2 h glucose concentration to define prediabetes was more likely to identify women, and less likely to identify black and obese people, but baseline risk factors were otherwise similar (**Table 2**). Characteristics of participants identified as having prediabetes using WHO fasting glucose concentration cutoffs and using IEC HbA1c cutoffs are shown in the appendix.

The prevalence of prediabetes varied between different definitions of prediabetes (**Table 3**). Cross-tabulation of the different definitions are shown in the appendix. Among 10844 participants included in the analyses for visit 2, 3152 incident cases of diabetes, 2608 incident cases of chronic kidney disease, 1556 incident atherosclerotic cardiovascular events, 266 incident cases of peripheral arterial disease, and 3177 deaths were reported in approximately 22 years of follow-up. Among 7194 participants included in the analyses for visit 4, 1859 incident cases of diabetes, 1444 incident cases of chronic kidney disease, 760 incident atherosclerotic cardiovascular events, 115 incident cases of peripheral arterial disease, and 1568 deaths were reported in approximately 16 years of follow-up (appendix). Comparison of the sensitivity and specificity for each definition of prediabetes for 10 year risk of each outcome showed that definitions using ADA and IEC HbA1c cutoffs, and WHO fasting glucose concentration cutoffs had higher specificity than ADA fasting glucose concentration cutoffs for all outcomes, whereas ADA fasting glucose concentration cutoffs, and ADA and WHO 2 h glucose concentration cutoffs, were more sensitive than WHO fasting glucose concentration cutoffs (**Table 4**). ADA and IEC HbA1c cutoffs, and WHO fasting glucose concentration cutoffs had higher positive predictive values and negative likelihood ratios for incident diabetes and higher positive likelihood ratios for all outcomes compared with ADA fasting glucose concentration cutoffs. Negative predictive values were numerically similar across outcomes.

In Cox proportional hazard models for age, sex, and, race centre, prediabetes by all five definitions was significantly associated with risk of future clinical outcomes (**Table 5**). In participants identified as having prediabetes using HbA1c -based

definitions, incidence rates were higher, hazard ratios were larger, and C-statistics for chronic kidney disease, atherosclerotic cardiovascular disease, peripheral arterial disease, and all-cause mortality were higher, than in participants identified using ADA and WHO fasting glucose concentration cutoffs (**Table 5**; appendix). Adjusting for additional risk factors did not alter our findings (appendix). The differences in the C-statistics between HbA1c-based definitions and glucose-based definitions, although statistically significant, were small (improvement in the C-statistic was generally less than 0.02). Prediabetes defined using ADA HbA1c cutoffs also showed significant overall improvement in the cNRI for atherosclerotic cardiovascular disease, peripheral arterial disease, and all-cause mortality compared to prediabetes defined using ADA and WHO fasting glucose concentration cutoffs (appendix). The cNRI results show that the improvement was modest and primarily driven by the correct reclassification of non-events, consistent with the higher specificity of the HbA1c-based definitions than the ADA fasting glucose concentration-based definition. For incident diabetes, after demographic adjustment, IEC HbA1c cutoffs had the largest hazard ratio, but the ADA fasting glucose concentration cutoffs had a significantly higher C-statistic and better classified people at risk for future incident diabetes based on overall cNRI improvement (**Table 5**; appendix). However, after adjustment for additional risk factors (fully adjusted model), no significant difference in the C-statistics for ADA fasting glucose clinical categories compared with the other definitions remained (appendix). The hazard ratios and C-statistics for all outcomes were similar when all ADA and WHO glucose prediabetes definitions were compared, with the exception of incident diabetes. Although the hazard ratio for WHO fasting glucose-defined prediabetes was higher, the C-statistic for ADA fasting glucose-

defined prediabetes was modestly, although significantly, improved for classification of people at risk of developing diabetes (**Table 5**; appendix). However, these differences did not persist after adjustment for additional risk factors (fully adjusted model).

Exclusion of people with undiagnosed diabetes did not alter our findings (appendix). We did not observe consistent differences in results across outcomes in analyses by race, with the exception of incident diabetes which was significantly different between black and white people (appendix). Across all definitions, black people were less likely to report a subsequent diagnosis of diabetes or glucose-lowering-medication use during follow-up than were white people in the demographic adjusted model (all p interaction <0.05; appendix). After adjustment for additional risk factors (fully adjusted model) the difference between black people and white people was reduced, although the interaction for some definitions (WHO fasting glucose concentration, IEC HbA1c, ADA HbA1c, and ADA and WHO 2 h glucose concentration) remained statistically significant (appendix). In analyses stratified by sex, a stronger association existed between prediabetes and undiagnosed diabetes with peripheral arterial disease in women than in men for both HbA1c-based and fasting glucose-based definitions (appendix). By contrast, ADA and WHO 2 h glucose was not significantly associated with incident peripheral arterial disease in men or women. Mortality associations, regardless of definition, were also stronger in women than in men. Our ancillary analysis in NHANES III (appendix) showed similar patterns in prevalence, sensitivity, and specificity for the different definitions of prediabetes. For all-cause mortality, patterns in hazard ratios and Harrell's C-statistic were also similar. For fatal cardiovascular disease, hazard ratios for prediabetes identified using IEC HbA1c cutoffs were the largest, followed by ADA

fasting glucose concentration cutoffs, ADA HbA1c cutoffs, ADA and WHO 2 h glucose concentration cutoffs, and WHO fasting glucose concentration cutoffs (appendix).

Discussion

In this cohort study, we showed that prevalence of prediabetes and performance of various definitions of prediabetes were significantly different when analysed in the context of long-term complications. Use of ADA fasting glucose concentration cutoffs or ADA and WHO 2 h glucose concentration cutoffs to define prediabetes resulted in higher prevalence estimates than did use of WHO fasting glucose concentration cutoffs, ADA HbA1c cutoffs, or IEC HbA1c cutoffs. With the ADA fasting glucose concentration definition, over a third of the study population was estimated to have prediabetes. ADA HbA1c cutoffs, IEC HbA1c cutoffs, and WHO fasting glucose concentration cutoffs were the most specific definitions for identification of people at risk for long-term clinical outcomes, resulting in higher positive likelihood ratios than the other definitions, whereas ADA fasting glucose concentration cutoffs and ADA and WHO 2 h glucose concentration cutoffs were more sensitive than ADA and IEC HbA1c cutoffs, and WHO fasting glucose concentration cutoffs. These differences in sensitivity and specificity are important for choosing a definition of prediabetes for use in a screening programme. Differences in risk discrimination across prediabetes definitions were modest, but clinical categories for prediabetes based on HbA1c (ADA or IEC) definitions performed slightly better than those based on fasting glucose concentrations for microvascular and macrovascular outcomes. Net reclassification improvement also supported prediabetes defined by ADA HbA1c cutoffs as a better classifier for people at risk of future cardiovascular and mortality outcomes. In minimally adjusted models, fasting glucose-

defined prediabetes was slightly better for prediction of future diabetes than HbA1c-defined prediabetes. This result is not surprising because most cases of diabetes would have been identified by a healthcare provider during follow-up on the basis of elevations in glucose concentrations since HbA1c was not recommended for use in diagnosis until 2009. Clinical categories defined using ADA fasting glucose concentration, WHO fasting glucose concentration, and ADA and WHO 2 h glucose concentration were generally similar for risk discrimination of clinical outcomes. Across all definitions of prediabetes, whether defined using fasting glucose concentration, HbA1c, or 2 h glucose concentration, black people were less likely to report a diagnosis of diabetes or diabetes medication use during follow-up. This suggests that for the same level of hyperglycaemia, black people might be more likely to have delays in diagnosis, reflecting disparities in socioeconomic status or access to care. There was little evidence for race interaction for the other clinical outcomes. Our findings complement existing evidence and extend previous findings in ARIC. One ARIC study[22] found that fasting glucose concentration of 5.6–6.9 mmol/L and 2 h glucose of 7.8–11.0 mmol/L had similar associations with incident cardiovascular disease and all-cause mortality during a median follow-up time of 6.3 years. Our results confirm these findings, but with approximately 10 more years of follow-up and more incident events. Our findings are also consistent with results from the Emerging Risk Factors Collaboration (ERFC),[23] a 73-study, participant-level meta-analysis of 294998 individuals. The ERFC study found that, compared with fasting glucose, random glucose, or postload glucose, HbA1c provided a small, but significant, improvement in the C-statistic for discrimination of cardiovascular disease risk. By contrast, in the 2001 DECODE study[24] of 22514 participants from ten

different European centres followed up for 8.8 years, 2 h glucose was more strongly associated with atherosclerotic cardiovascular death and all-cause mortality than was fasting glucose concentration. We do note that measurements in different blood specimens (plasma, whole blood) were collected in DECODE across the ten European centres. Methodological and study population differences notwithstanding, the reasons why our results do not agree with the DECODE findings are unclear. Meta-analyses[25,26] have also shown conflicting results for whether impaired fasting glucose or impaired glucose tolerance is more strongly associated with cardiovascular disease outcomes.

Several limitations of our study should be considered in the interpretation of our findings. First, we did not have concurrent measurements of fasting glucose, HbA1c, and 2 h glucose, and all classifications were based on single measurements whereas in clinical practice, these measurements might be repeated. In practice, clinical decisions are based on a compendium of laboratory, clinical, and epidemiological information. Nonetheless, for prediabetes, there are currently no formal recommendations or consensus regarding repeating tests for confirmation. Second, as part of the ARIC study protocol, abnormal laboratory values including raised fasting glucose concentration (>11.1 mmol/L) or 2 h glucose (>16.7 mmol/L) were reported back to the participants, although less than 1.5% of participants had elevated values that prompted a report. HbA1c results at visit 2 were not reported to participants as they were measured retrospectively (>10 years after sample collection). The reporting of the glucose measures to participants might have increased the probability of a diagnosis of diabetes.[27] Third, we used a definition of incident diabetes based on self-report. Fourth, our findings might not be generalisable beyond black and white Americans. Fifth, despite the large sample size and number of events, the

possibility exists that the study might have been underpowered to detect moderate differences between definitions, particularly given the overlap of definitions. Finally, although our results in ARIC were consistent with findings for all-cause and cardiovascular mortality in NHANES III, further replication, especially for other major complications in diverse populations, is needed. The strengths of this study include our ability to compare the prognostic value of multiple definitions of prediabetes, rigorous assessment of hyperglycaemia and related risk factors with standardised protocols and trained personnel, active surveillance for major clinical complications, and over two decades of follow-up in a large, community-based population. A number of considerations need to be weighed when deciding between definitions of prediabetes for screening programmes, and the optimal choice will depend on objectives. Long-term risk associations, along with considerations such as cost, availability, and the specific strengths and weaknesses of each biomarker, are all relevant. It is difficult to establish whether a strategy that would identify large numbers of people, including many people at low risk of future outcomes, might be more beneficial than strategies that are highly specific, but might miss some high-risk individuals who should receive preventive interventions. Prediabetes defined by ADA and IEC HbA1c cutoffs, and WHO fasting glucose concentration cutoffs identified fewer people, but these definitions were more specific for the identification of people at risk for long-term outcomes. HbA1c-based definitions had higher relative risk associations and showed small, but statistically significant, improvements in risk discrimination for a broad range of clinical complications. Whereas prediabetes defined by ADA fasting glucose concentration cutoffs was more sensitive, it was not as strongly associated with long-term risk of

clinical complications. For long-term prediction of clinical outcomes, prediabetes definitions based on 2 h glucose concentration did not better predict the risk of chronic kidney disease or cardiovascular outcomes than fasting glucose concentration. The comparative usefulness of different definitions of prediabetes will vary depending on the goals of the screening programme; however, data on long-term prognostic performance can, and should, help to inform use of and recommendations for different definitions of prediabetes.

Table 1. Baseline characteristics of ARIC participants (Visit 2, 1990-92) without a history of cardiovascular disease or diagnosed diabetes by different definitions of prediabetes*

	Normoglycemia	Prediabetes	Undiagnosed diabetes	Normoglycemia	Prediabetes	Undiagnosed diabetes
	ADA fasting glucose clinical categories			ADA HbA1c clinical categories		
Visit 2 (1990-92) N = 10,844	**<5.6 mmol/L n = 6,215**	**5.6-6.9 mmol/L n = 4,112**	**≥7.0 mmol/L n = 517**	**<39 mmol/mol n = 8,355**	**39-46 mmol/mol n = 2,027**	**≥48 mmol/mol n = 462**
Age (years)	56.8 (5.6)	57.6 (5.7)	57.7 (5.6)	56.8 (5.6)	58.2 (5.6)	58.1 (5.6)
Female, %	63.2	47.8	54.4	57.4	54.2	61.5
Black, %	17.3	25.1	37.3	15.0	40.4	49.8
Less than high school education, %	16.3	21.3	28.1	15.6	28.9	32.3
Body Mass Index (kg/m^2)	26.4 (4.8)	28.9 (5.2)	31.6 (6.1)	27.0 (4.8)	29.3 (5.8)	32.3 (6.3)
Obese (≥30 kg/m^2), %	18.8	34.5	54.4	21.7	38.4	59.5
Waist-to-hip ratio	0.90 (0.1)	0.94 (0.1)	0.97 (0.1)	0.91 (0.1)	0.94 (0.1)	0.97 (0.1)
Fasting glucose (mmol/L)	5.11 (0.3)	5.98 (0.4)	8.62 (2.5)	5.39 (0.5)	5.89 (0.7)	8.29 (2.9)
HbA1c (mmol/mol)	34.9 (4.2)	37.6 (4.8)	52.7 (17)	34.3 (3.1)	41.9 (1.9)	57.6 (15.6)
Hypercholesterolemia, %	74.0	81.7	87.6	75.8	82.8	87.9
Hypertension, %	24.5	37.8	54.6	26.9	42.4	53.9
Estimated glomerular filtration rate (mL/min/1.73 m^2)	97.3 (13)	96.9 (14)	99.7 (15)	96.8 (13)	98.2 (15)	101 (16)
Current smoker, %	21.6	21.6	19.7	19.8	27.9	23.6
Current drinker, %	60.8	59.2	54.2	63.3	50.0	41.8
Family history of diabetes, %	20.3	24.6	33.7	21.3	25.2	34.0

* Mean (SD) unless otherwise indicated

Abbreviations: ADA, American Diabetes Association; HbA1c, hemoglobin A1c; WHO, World Health Organization

Table 2. Baseline characteristics of ARIC participants (Visit 4, 1996-98) without a history of cardiovascular disease or diagnosed diabetes by different definitions of prediabetes*

	Normoglycemia	Prediabetes	Undiagnosed diabetes	Normoglycemia	Prediabetes	Undiagnosed diabetes
	ADA fasting glucose clinical categories			ADA/WHO 2-hour glucose clinical categories		
Visit 4 (1996-98)	**<5.6 mmol/L**	**5.6-6.9 mmol/L**	**≥7.0 mmol/L**	**<7.8 mmol/L**	**7.8-11.0 mmol/L**	**≥11.0 mmol/L**
N = 7,194	**n = 4,720**	**n = 2,142**	**n = 332**	**n = 4,442**	**n = 2,009**	**n = 743**
Age (years)	62.7 (5.5)	62.9 (5.5)	63.1 (5.4)	62.1 (5.4)	63.6 (5.6)	64.3 (5.5)
Female, %	63.2	47.8	51.8	55.4	62.5	62.1
Black, %	14.5	21.2	25.6	17.1	15.4	20.5
Less than high school education, %	13.6	18.2	23.2	13.6	17.0	21.7
Body Mass Index (kg/m^2)	27.4 (5.0)	30.1 (5.3)	32.1 (6.0)	27.7 (5.1)	29.2 (5.3)	30.5 (5.6)
Obese (≥30 kg/m^2), %	24.0	45.1	60.2	26.2	38.5	48.7
Waist-to-hip ratio	0.93 (0.1)	0.97 (0.1)	0.98 (0.1)	0.93 (0.1)	0.95 (0.1)	0.97 (0.1)
Fasting glucose (mmol/L)	5.09 (0.3)	6.00 (0.3)	8.72 (2.5)	5.26 (0.5)	5.54 (0.6)	7.06 (2.3)
2-hour glucose (mmol/L)	6.76 (2.0)	8.23 (2.5)	14.8 (4.3)	5.84 (1.1)	9.10 (0.9)	13.7 (3.0)
Hypercholesterolemia, %	73.6	82.5	87.7	73.4	81.0	86.7
Hypertension, %	36.1	47.8	60.5	34.3	47.9	59.5
Estimated glomerular filtration rate (mL/min/1.73 m^2)	88.2 (12)	88.3 (13)	89.6 (12)	88.1 (12)	88.5 (13)	88.7 (13)
Current smoker, %	14.0	14.4	11.8	15.6	11.7	10.8
Current drinker, %	55.2	55.3	49.1	57.8	51.7	46.7
Family history of diabetes, %	19.8	26.3	33.1	19.2	26.2	30.8

* Mean (SD) unless otherwise indicated

Abbreviations: ADA, American Diabetes Association; HbA1c, hemoglobin A1c; WHO, World Health Organization

Table 3. Prevalence (95% confidence interval) of prediabetes by definition

	Prevalence (95%CI)
Visit 2 (1990-92)	
ADA fasting glucose, 5.6-6.9 mmol/L	37.9 (37.0, 38.8)
WHO fasting glucose, 6.1-6.9 mmol/L	11.2 (10.6, 11.8)
ADA HbA1c, 39-46 mmol/mol	18.7 (18.0, 19.4)
IEC HbA1c, 42-46 mmol/mol	8.95 (8.42, 9.50)
Visit 4 (1996-98)	
ADA fasting glucose, 5.6-6.9 mmol/L	29.8 (28.7, 30.8)
WHO fasting glucose, 6.1-6.9 mmol/L	8.63 (8.00, 9.30)
ADA/WHO 2-hour glucose, 7.8-11.0 mmol/L	27.9 (26.9, 29.0)

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; IEC, International Expert Committee; WHO, World Health Organization

Table 4. 10-year sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio and corresponding 95% confidence intervals of incident clinical outcomes according to different definitions of prediabetes (vs. normoglycemia) at baseline

Outcome	Visit 2 (1990-92)				Visit 4 (1996-98)		
	ADA fasting glucose 5.6-6.9 mmol/L	WHO fasting glucose 6.1-6.9 mmol/L	ADA HbA1c 39-46 mmol/mol	IEC HbA1c 42-46 mmol/mol	ADA fasting glucose 5.6-6.9 mmol/L	WHO fasting glucose 6.1-6.9 mmol/L	ADA/WHO 2-hour glucose 7.8-11.0 mmol/L
Incident diabetes							
Sensitivity	0.73 (0.70, 0.76)	0.41 (0.37, 0.44)	0.52 (0.49, 0.55)	0.34 (0.31, 0.37)	0.61 (0.58, 0.64)	0.28 (0.26, 0.31)	0.55 (0.51, 0.58)
Specificity	0.63 (0.62, 0.64)	0.91 (0.90, 0.91)	0.83 (0.83, 0.84)	0.93 (0.92, 0.93)	0.74 (0.73, 0.75)	0.94 (0.94, 0.95)	0.72 (0.71, 0.73)
PPV	0.15 (0.14, 0.16)	0.28 (0.26, 0.31)	0.22 (0.21, 0.24)	0.31 (0.28, 0.34)	0.28 (0.26, 0.30)	0.44 (0.40, 0.48)	0.21 (0.20, 0.23)
NPV	0.96 (0.96, 0.97)	0.95 (0.94, 0.95)	0.95 (0.95, 0.96)	0.94 (0.93, 0.94)	0.92 (0.91, 0.93)	0.89 (0.88, 0.90)	0.92 (0.91, 0.93)
+LR	1.98 (1.89, 2.08)	4.41 (3.97, 4.89)	3.14 (2.90, 3.39)	4.81 (4.28, 5.41)	2.34 (2.19, 2.50)	4.84 (4.19, 5.58)	1.96 (1.82, 2.12)
-LR	0.43 (0.38, 0.48)	0.66 (0.64, 0.69)	0.58 (0.54, 0.62)	0.71 (0.68, 0.74)	0.52 (0.48, 0.57)	0.76 (0.73, 0.79)	0.63 (0.58, 0.68)
Chronic kidney disease							
Sensitivity	0.48 (0.43, 0.53)	0.18 (0.14, 0.23)	0.31 (0.27, 0.37)	0.15 (0.11, 0.19)	0.37 (0.31, 0.44)	0.15 (0.11, 0.20)	0.32 (0.26, 0.39)
Specificity	0.61 (0.60, 0.61)	0.89 (0.88, 0.89)	0.81 (0.80, 0.82)	0.91 (0.90, 0.91)	0.69 (0.68, 0.70)	0.91 (0.91, 0.92)	0.69 (0.68, 0.70)
PPV	0.04 (0.04, 0.05)	0.05 (0.04, 0.07)	0.05 (0.05, 0.07)	0.05 (0.04, 0.07)	0.04 (0.03, 0.05)	0.06 (0.04, 0.08)	0.03 (0.03, 0.04)
NPV	0.97 (0.97, 0.97)	0.97 (0.96, 0.97)	0.97 (0.97, 0.97)	0.97 (0.96, 0.97)	0.97 (0.96, 0.97)	0.97 (0.96, 0.97)	0.97 (0.96, 0.97)
+LR	1.21 (1.08, 1.35)	1.58 (1.27, 1.98)	1.64 (1.40, 1.92)	1.60 (1.24, 2.08)	1.20 (1.01, 1.42)	1.72 (1.26, 2.35)	1.03 (0.85, 1.26)
-LR	0.86 (0.78, 0.95)	0.92 (0.88, 0.97)	0.85 (0.79, 0.91)	0.94 (0.90, 0.98)	0.91 (0.83, 1.01)	0.93 (0.88, 0.98)	0.99 (0.90, 1.08)
Atherosclerotic cardiovascular disease							
Sensitivity	0.47 (0.43, 0.52)	0.16 (0.13, 0.19)	0.34 (0.30, 0.39)	0.18 (0.15, 0.21)	0.39 (0.34, 0.44)	0.12 (0.09, 0.16)	0.32 (0.28, 0.37)
Specificity	0.61 (0.60, 0.62)	0.89 (0.88, 0.89)	0.81 (0.81, 0.82)	0.91 (0.91, 0.92)	0.69 (0.68, 0.70)	0.91 (0.90, 0.92)	0.69 (0.68, 0.70)
PPV	0.06 (0.06, 0.07)	0.07 (0.06, 0.09)	0.09 (0.08, 0.11)	0.10 (0.08, 0.12)	0.07 (0.06, 0.08)	0.07 (0.06, 0.10)	0.06 (0.05, 0.07)
NPV	0.95 (0.95, 0.96)	0.95 (0.94, 0.95)	0.96 (0.95, 0.96)	0.95 (0.95, 0.96)	0.95 (0.94, 0.95)	0.94 (0.94, 0.95)	0.95 (0.94, 0.95)
+LR	1.20 (1.10, 1.32)	1.36 (1.11, 1.66)	1.84 (1.63, 2.08)	2.03 (1.68, 2.45)	1.25 (1.10, 1.43)	1.36 (1.03, 1.79)	1.04 (0.89, 1.21)
-LR	0.87 (0.80, 0.94)	0.95 (0.92, 0.99)	0.81 (0.76, 0.86)	0.90 (0.87, 0.94)	0.89 (0.82, 0.96)	0.97 (0.93, 1.00)	0.98 (0.91, 1.06)

Abbreviations: ADA, American Diabetes Association; IEC, International Expert Committee; HbA1c, hemoglobin A1c; PPV, positive predictive value; NPV, negative predictive value; WHO, World Health Organization; +LR, positive likelihood ratio, -LR, negative likelihood ratio

Table 4., continued

Outcome	Visit 2 (1990-92)				Visit 4 (1996-98)		
	ADA fasting glucose 5.6-6.9 mmol/L	WHO fasting glucose 6.1-6.9 mmol/L	ADA HbA1c 39-46 mmol/mol	IEC HbA1c 42-46 mmol/mol	ADA fasting glucose 5.6-6.9 mmol/L	WHO fasting glucose 6.1-6.9 mmol/L	ADA/WHO 2-hour glucose 7.8-11.0 mmol/L
Peripheral arterial disease							
Sensitivity	0.54 (0.41, 0.66)	0.19 (0.11, 0.31)	0.30 (0.20, 0.43)	0.14 (0.06, 0.24)	0.42 (0.29, 0.57)	0.08 (0.02, 0.19)	0.37 (0.24, 0.51)
Specificity	0.60 (0.59, 0.61)	0.88 (0.88, 0.89)	0.81 (0.80, 0.81)	0.91 (0.90, 0.91)	0.69 (0.68, 0.70)	0.91 (0.90, 0.92)	0.69 (0.68, 0.70)
PPV	0.01 (0.01, 0.01)	0.01 (0.01, 0.02)	0.01 (0.01, 0.02)	0.01 (0.00, 0.02)	0.01 (0.01, 0.02)	0.01 (0.00, 0.02)	0.01 (0.01, 0.01)
NPV	1.00 (0.99, 1.00)	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	0.99 (0.99, 0.99)	0.99 (0.99, 1.00)
+LR	1.35 (1.08, 1.69)	1.66 (1.02, 2.71)	1.56 (1.08, 2.25)	1.46 (0.80, 2.69)	1.36 (0.99, 1.87)	0.85 (0.33, 2.18)	1.17 (0.82, 1.68)
-LR	0.77 (0.59, 0.99)	0.91 (0.81, 1.03)	0.87 (0.74, 1.01)	0.95 (0.87, 1.05)	0.84 (0.66, 1.06)	1.02 (0.94, 1.10)	0.92 (0.75, 1.13)
All-cause mortality							
Sensitivity	0.46 (0.42, 0.49)	0.15 (0.12, 0.17)	0.31 (0.27, 0.35)	0.16 (0.13, 0.18)	0.35 (0.31, 0.39)	0.13 (0.10, 0.15)	0.33 (0.29, 0.37)
Specificity	0.61 (0.60, 0.62)	0.89 (0.88, 0.89)	0.81 (0.81, 0.82)	0.91 (0.91, 0.92)	0.69 (0.68, 0.70)	0.91 (0.91, 0.92)	0.69 (0.68, 0.70)
PPV	0.08 (0.07, 0.08)	0.08 (0.07, 0.10)	0.11 (0.09, 0.12)	0.11 (0.09, 0.13)	0.10 (0.08, 0.11)	0.12 (0.10, 0.15)	0.09 (0.08, 0.11)
NPV	0.94 (0.93, 0.95)	0.94 (0.93, 0.94)	0.94 (0.94, 0.95)	0.94 (0.93, 0.94)	0.92 (0.91, 0.92)	0.92 (0.91, 0.92)	0.92 (0.91, 0.93)
+LR	1.15 (1.06, 1.26)	1.26 (1.04, 1.53)	1.65 (1.46, 1.86)	1.74 (1.45, 2.10)	1.12 (0.99, 1.25)	1.43 (1.14, 1.80)	1.07 (0.95 1.21)
-LR	0.90 (0.84, 0.97)	0.97 (0.94, 1.00)	0.85 (0.81, 0.90)	0.93 (0.90, 0.96)	0.95 (0.89, 1.01)	0.96 (0.93, 0.99)	0.97 (0.91, 1.03)

Abbreviations: ADA, American Diabetes Association; IEC, International Expert Committee; HbA1c, hemoglobin A1c; PPV, positive predictive value; NPV, negative predictive value; WHO, World Health Organization; +LR, positive likelihood ratio, -LR, negative likelihood ratio

Table 5. Demographic adjusted hazard ratio and Harrell's C-statistic (95% confidence intervals) for incident outcomes by different clinical categories of prediabetes and undiagnosed diabetes

Visit 2 (1990-92)		Incident diabetes	Chronic kidney disease	Atherosclerotic cardiovascular disease	Peripheral arterial disease	All-cause mortality
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	2.91 (2.69, 3.15)*	1.17 (1.08, 1.27)*	1.24 (1.12, 1.38)*	1.34 (1.03, 1.74)*	1.12 (1.04, 1.21)*
	≥7.0 mmol/L‡	19.7 (17.6, 22.2)*	1.75 (1.49, 2.05)*	2.10 (1.74, 2.53)*	3.40 (2.30, 5.01)*	1.55 (1.35, 1.79)*
	C-statistic (95% CI)	0.713 (0.704, 0.723)	0.636 (0.625, 0.647)	0.662 (0.649, 0.676)	0.701 (0.670, 0.733)	0.683 (0.674, 0.692)
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	3.81 (3.48, 4.16)*	1.28 (1.14, 1.43)*	1.22 (1.05, 1.41)*	1.35 (0.95, 1.92)	1.25 (1.13, 1.38)*
	≥7.0 mmol/L‡	14.5 (13.0, 16.2)*	1.69 (1.45, 1.97)*	1.95 (1.63, 2.34)*	3.09 (2.14, 4.47)*	1.52 (1.32, 1.75)*
	C-statistic (95% CI)	0.693 (0.683, 0.703)	0.636 (0.625, 0.647)	0.660 (0.646, 0.673)	0.700 (0.668, 0.732)	0.683 (0.674, 0.693)
ADA HbA1c definition	<39 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	39-46 mmol/mol	3.42 (3.15, 3.72)*	1.42 (1.29, 1.57)*	1.70 (1.51, 1.92)*	1.84 (1.37, 2.47)*	1.49 (1.37, 1.62)*
	≥48 mmol/mol‡	20.8 (18.4, 23.4)*	2.04 (1.73, 2.40)*	2.40 (1.98, 2.90)*	5.38 (3.75, 7.73)*	1.81 (1.57, 2.10)*
	C-statistic (95% CI)	0.693 (0.683, 0.703)	0.640 (0.629, 0.651)	0.672 (0.659, 0.685)	0.722 (0.690, 0.754)	0.688 (0.679, 0.697)
IEC HbA1c definition	<42 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	42-46 mmol/mol	4.14 (3.74, 4.58)*	1.50 (1.32, 1.70)*	1.91 (1.65, 2.21)*	1.95 (1.34, 2.82)*	1.56 (1.40, 1.73)*
	≥48 mmol/mol‡	17.9 (15.9, 20.2)*	1.96 (1.67, 2.30)*	2.27 (1.88, 2.74)*	4.99 (3.49, 7.11)*	1.73 (1.50, 1.99)*
	C-statistic (95% CI)	0.669 (0.659, 0.680)	0.639 (0.628, 0.650)	0.668 (0.655, 0.682)	0.718 (0.686, 0.750)	0.687 (0.678, 0.696)

Adjusted for age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; IEC, International Expert Committee; HbA1c, hemoglobin A1c; HR, hazard ratio; WHO, World Health Organization

Outcome Definitions: Incident diabetes: self-report of a physician diagnosis of diabetes or use of glucose-lowering medication during a study visit or annual telephone call; Chronic kidney disease: subsequent estimated glomerular filtration rate (eGFR) measurement < 60 mL/min/1.73 m^2 measured at a study visit and an eGFR decline from baseline visit of at least 25% at the follow-up visit, or chronic kidney disease related hospitalization or death, or an end stage renal disease event identified by the United States Renal Data System registry; Atherosclerotic cardiovascular disease: any coronary heart disease hospitalization and death and ischemic stroke hospitalization and death (adjudicated events); Peripheral arterial disease: events identified from hospitalization records (International Classification of Disease, Ninth Revision (ICD-9) discharge codes) for peripheral arterial disease (440.2, 440.3, 440.4) or leg revascularization (38.18, 39.25, 39.29, 39.50); All-cause mortality: ascertained from hospital and National Death Index records

Table 5., continued

Visit 4 (1996-98)		Incident diabetes	Chronic kidney disease	Atherosclerotic cardiovascular disease	Peripheral arterial disease	All-cause mortality
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	3.43 (3.10, 3.80)*	1.08 (0.96, 1.21)	1.25 (1.07, 1.45)*	1.09 (0.73, 1.63)	1.15 (1.03, 1.28)*
	≥7.0 mmol/L‡	25.3 (21.9, 29.2)*	1.45 (1.16, 1.82)*	1.79 (1.36, 2.37)*	1.99 (1.02, 3.88)*	1.68 (1.37, 2.05)*
	C-statistic (95% CI)	0.726 (0.714, 0.738)	0.624 (0.609, 0.639)	0.660 (0.641, 0.680)	0.707 (0.660, 0.754)	0.686 (0.673, 0.699)
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	4.48 (3.97, 5.05)*	1.23 (1.04, 1.47)*	1.10 (0.87, 1.40)	0.63 (0.29, 1.35)	1.29 (1.10, 1.51)*
	≥7.0 mmol/L‡	18.5 (16.2, 21.2)*	1.45 (1.16, 1.81)*	1.67 (1.27, 2.20)*	1.85 (0.96, 3.56)	1.65 (1.35, 2.01)*
	C-statistic (95% CI)	0.694 (0.681, 0.708)	0.625 (0.610, 0.640)	0.658 (0.638, 0.677)	0.710 (0.662, 0.757)	0.687 (0.673, 0.700)
ADA / WHO 2-hour glucose definition	<7.8 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	7.8-11.0 mmol/L	2.56 (2.30, 2.86)*	1.16 (1.03, 1.31)*	1.08 (0.92, 1.27)	0.83 (0.54, 1.29)	1.17 (1.05, 1.31)*
	≥11.0 mmol/L‡	10.6 (9.41, 11.9)*	1.39 (1.18, 1.63)*	1.44 (1.17, 1.78)*	0.93 (0.50, 1.72)	1.33 (1.15, 1.55)*
	C-statistic (95% CI)	0.728 (0.716, 0.741)	0.626 (0.611, 0.641)	0.659 (0.639, 0.678)	0.705 (0.658, 0.752)	0.685 (0.672, 0.698)

Adjusted for age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; IEC, International Expert Committee; HbA1c, hemoglobin A1c; HR, hazard ratio; WHO, World Health Organization

Outcome Definitions: Incident diabetes: self-report of a physician diagnosis of diabetes or use of glucose-lowering medication during a study visit or annual telephone call; Chronic kidney disease: subsequent estimated glomerular filtration rate (eGFR) measurement < 60 mL/min/1.73 m^2 measured at a study visit and an eGFR decline from baseline visit of at least 25% at the follow-up visit, or chronic kidney disease related hospitalization or death, or an end stage renal disease event identified by the United States Renal Data System registry; Atherosclerotic cardiovascular disease: any coronary heart disease hospitalization and death and ischemic stroke hospitalization and death (adjudicated events); Peripheral arterial disease: events identified from hospitalization records (International Classification of Disease, Ninth Revision (ICD-9) discharge codes) for peripheral arterial disease (440.2, 440.3, 440.4) or leg revascularization (38.18, 39.25, 39.29, 39.50); All-cause mortality: ascertained from hospital and National Death Index records

Chapter 3. Diagnostic performance of 1,5-anhydroglucitol compared to 2-hour glucose in the Atherosclerosis Risk in Communities Study

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Abstract

Background: Glucose measured two hours after a carbohydrate challenge (2-hour glucose) has long been a gold standard for diabetes diagnosis, but it has fallen out of favor primarily due to the high patient burden and the availability of alternative diagnostic markers. Plasma concentrations of 1,5-anhydroglucitol (1,5-AG) decrease in response to hyperglycemia, and thus low 1,5-AG may be a less burdensome biomarker of hyperglycemic excursions. However, few studies have directly compared 2-hour glucose and 1,5-AG in a community-based setting.

Methods: We conducted a cross-sectional analysis of 7,813 Atherosclerosis Risk in Community (ARIC) Study participants without diagnosed diabetes who attended the 1996-98 visit, when both 2-hour glucose and 1,5-AG were measured. We examined diagnostic performance of low 1,5-AG (<10 μg/mL, <12 μg/mL, or <16 μg/mL) to detect elevated 2-hour glucose as the gold standard (≥200 mg/dL).

Results: The proportion of the population with elevated 2-hour glucose, or 1,5-AG <10 μg/mL was 10.5%, and 5.6%, respectively. 3.5% of participants had 1,5-AG <10 μg/mL without glucose elevations (false positives). Comparing the diagnostic performance of 1,5-AG<10 μg/mL to 2-hour glucose ≥200 mg/dL resulted in a sensitivity of 19.4% (95% CI, 16.8, 22.3) and specificity of 96.1% (95% CI, 95.6, 96.5). Higher cut-points of 1,5-

AG resulted in higher sensitivity but lower specificity for detecting elevations in 2-hour glucose. The area under the ROC curve comparing 1,5-AG <10 μg/mL to elevated 2-hour glucose was 0.66. False positive results were associated with decreased kidney function and kidney damage.

Conclusions: Although less burdensome from the patient perspective, 1,5-AG is unlikely to be useful for diabetes screening in the general U.S. population, although the high specificity of 1,5-AG may help to identify very high-risk individuals. The large proportion of false positives suggests further research is needed to understand the determinants of 1,5-AG beyond glycemic excursions.

Introduction

In 2015, approximately 1.5 million people in the United States were diagnosed with diabetes[1,2].The measurement of 2-hour glucose following a 75-g oral glucose tolerance test has been a long-standing "gold standard" for diagnosis of diabetes and was first recommended by the National Diabetes Data Group in 1979[3–7]. However, given the high patient burden along with its high within-person variability[8], 2-hour glucose has fallen out of favor in clinical practice as a primary diagnostic tool, mostly supplanted by fasting glucose and hemoglobin A1c (HbA1c), which measure slightly different aspects of glucose control[9].

While evidence is preliminary and conflicting, some prior studies have suggested that 1,5-anhydroglucitol (1,5-AG) may have utility as a screening test for diabetes with similar performance to 2-hour fasting glucose[10–12]. 1,5-AG is a monosaccharide (the 1-deoxy form of glucose), primarily acquired through diet[13]. In states of euglycemia, concentrations of 1,5-AG remain at steady state in the blood. In states of overt

hyperglycemia, where glucose exceeds the renal threshold (typically >160-180 mg/dL), 1,5-AG competes with glucose for reabsorption in the renal proximal tubule and is excreted in the urine, resulting in lowered concentrations in the blood[14]. Therefore, low blood concentrations of 1,5-AG reflect recent glycemic excursions above the renal threshold. Unlike 2-hour glucose, 1,5-AG does not require fasting, a carbohydrate challenge, or multiple blood draws.

The objective of this study was to quantify the concordance of 1,5-AG with 2-hour glucose and evaluate its utility as a test to screen or diagnose diabetes. The concurrent measurements of 2-hour glucose and 1,5-AG in the Atherosclerosis Risk in Communities (ARIC) Study, a large community-based cohort study in the United States, presents a unique opportunity to formally compare these biomarkers, as well as with fasting glucose measures, the most commonly used index for the identification of persons with diabetes.

Methods

Study Population

The ARIC Study recruited 15,792 participants beginning in 1987 from four communities (Washington County, Maryland; Minneapolis, Minnesota; Jackson, Mississippi; and Forsyth County, North Carolina)[15]. To date, six study visits through 2017 have been completed. Institutional review boards provided necessary study approvals and all participants gave informed consent. We conducted a cross-sectional analysis using data collected from ARIC participants who attended the fourth study visit, which occurred from 1996 to 1998, when both 2-hour glucose and 1,5-AG were measured. Of the 11,656 participants in attendance, we excluded participants if they had a

history of diabetes at or before the fourth visit defined as a self-report of a physician diagnosis of diabetes or self-report of medications for diabetes (n=1,511), were missing 2-hour glucose, fasting glucose, or 1,5-AG measurements (n=2,251), did not fast for 10 or more hours (n=33), or were not black or white race or black from the Minnesota or Washington County sites (n=48; **Figure D-1**). Thus, our final study sample included 7,813 participants.

Measurement of Biomarkers of Hyperglycemia

A questionnaire was administered to participants to determine their eligibility for the oral glucose tolerance test during the fourth study visit. Participants were excluded from taking the glucose challenge if they had been treated for diabetes at the third ARIC visit or were taking diabetes medications, had prior surgery to remove part of the stomach or intestines, were on kidney dialysis, did not fast 10 hours or more, or were not willing to participate[16]. Two-hour glucose was measured in plasma following a 75-g oral glucose tolerance test and measurements were considered invalid if participants did not consume the glucola solution within 10 minutes, finish all of the solution (residual amount ≥145 ml), if information on blood draw timing was not available, or if blood was not drawn within 110-130 minutes of consumption of the solution.

Fasting plasma glucose was measured prior to the administration of the glucose tolerance test. Samples were analyzed at the Baylor College of Medicine using an enzymatic method on the Roche Hitachi 911 machine.

1,5-AG (GlycoMark) was measured in 2015-2016 in stored plasma samples from the fourth study visit at Baylor College of Medicine using the Beckman AU480 Chemistry Analyzer. The inter-assay coefficient of variation was 4.54%.

HbA1c was not available at the fourth ARIC visit. However, HbA1c was measured in stored whole blood samples from the second study visit (6 years earlier) using high-performance liquid chromatography methods certified by the National Glycohemoglobin Standardization Program and aligned to the Diabetes Control and Complications Trial assay[17]. In a secondary analysis, we compared HbA1c to 1,5-AG and fasting glucose values measured from samples taken at the same time point (second study visit, 1990-1992). 1,5-AG measurements from the second study visit were measured in 2012-2013 at University of Minnesota using a Roche Modular P800 system. Fasting glucose values at the second study visit were measured in serum at University of Minnesota using the Coulter DACOS machine.

Detection of Hyperglycemia

We evaluated the diagnostic performance of 1,5-AG relative to clinical cut-points for hyperglycemia based on current diabetes clinical practice guidelines[2]. We examined categories of hyperglycemia (considered gold standards) defined by an elevated 2-hour glucose (≥200 mg/dL), a fasting glucose (≥126 mg/dL), or both elevated 2-hour glucose and fasting glucose[2,18]. In secondary analyses, we used 1,5-AG and HbA1c measurements from visit 2 (6 years prior) to compare 1,5-AG to elevated HbA1c (≥6.5%) and hyperglycemia based on HbA1c ≥6.5% and fasting glucose ≥126 mg/dL[18]. Outcome definitions are shown in **Table D-1**.

Covariate Assessment

Age, sex (male or female), race (black or white), parental history of diabetes (yes or no), and education level (less than high school, high school graduate or vocational school, college education or higher) were self-reported at the first study visit. Dietary

intake, including dairy and bread and/or rice consumption, was assessed at the third study visit. Participants self-reported the number of servings they consumed on average for various foods[19]. All other covariates were assessed at the fourth study visit. Anthropometric measurements including height, weight, and waist-to-hip ratio were measured using standard protocols and body mass index was calculated as kilograms of weight divided by height in meters squared. Lipids (total cholesterol, HDL cholesterol, triglycerides) were obtained using standard methods. Systolic and diastolic blood pressures were assessed with systematic protocols and the first two measurements of each were averaged. Smoking status (current, former, never) and drinking status (current, former, never) were self-reported[16]. Creatinine was measured in plasma and used to estimate glomerular filtrate rate (eGFR) with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[20]. Albumin and creatinine were measured in urine samples[21] and albumin-to-creatinine ratio (ACR) was calculated. Liver enzymes (Alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) were also assessed.

Race-center was defined as 5-level variable combining race and study center, given race may be confounded with study center because of the ARIC Study design (Washington County, Maryland-White; Minneapolis, Minneapolis-White; Forsyth County, North Carolina-White; Forsyth County, North Carolina-Black; Jackson, Mississippi-Black). Servings of dairy products were combined into a dairy intake variable and categorized into tertiles of consumption. Similarly servings of bread and/or rice products were combined into a bread and rice intake variable and divided into tertiles. Hypertension was defined as mean systolic blood pressure ≥140 mmHg, mean diastolic blood pressure ≥90 mmHg, or self-report of blood pressure lowering medication use.

Chronic kidney disease was defined by Kidney Disease Improving Global Outcomes (KDIGO) guidelines stage G3b, G4, or G5 (eGFR <45ml/min/1.73m^2)[22]. Elevated levels of liver enzymes were defined using lab provided cutoffs (ALT >38.1 U/L or AST >44.4 U/L).

Statistical Analysis

In our main analyses, we categorized low 1,5-AG using the manufacturer-suggested threshold (1,5-AG <10 μg/mL). However, because there is currently no universally agreed-upon cut-point for this novel biomarker, we also defined low 1,5-AG using the percentile equivalents of a 2-hour glucose of 200 mg/dL (90 percentile; 1,5-AG <12 μg/mL) or a fasting glucose of 126 mg/dL (95 percentile; 1,5-AG <10 μg/mL), and calculated Youden's index from non-parametric ROC curves (1,5-AG <16 μg/mL), rounding each identified value to the nearest integer.

We compared clinical characteristics of the participants according to different definitions of hyperglycemia and low 1,5-AG (<10 μg/mL) using *t*-tests for means and Pearson's Chi squared tests for proportions. We evaluated the prevalence of elevated 2-hour glucose, elevated fasting glucose, and both elevated 2-hour glucose and fasting glucose and assessed their concordance with the prevalence of low 1,5-AG (<10 μg/mL) using a Venn Diagram. This analysis resulted in the identification of true negative results, those without hyperglycemia (2-hour <200 mg/dL and fasting glucose <126 mg/dL) and 1,5-AG ≥10 μg/mL; false positive results, those without hyperglycemia (2-hour <200 mg/dL and fasting glucose <126 mg/dL) and 1,5-AG <10 μg/mL; false negative results, those with hyperglycemia (2-hour ≥200 mg/dL and/or fasting glucose ≥126 mg/dL) and

1,5-AG ≥10 µg/mL; and true positive results, those with hyperglycemia (2-hour ≥200 mg/dL and/or fasting glucose ≥126 mg/dL) and 1,5-AG <10 µg/mL.

To investigate the ability of 1,5-AG to detect states of hyperglycemia in this population of individuals without diagnosed diabetes, we calculated sensitivity, specificity, positive and negative likelihood ratios, and positive and negative predictive values. We generated scatterplots and calculated Pearson's and Spearman's correlations of 1,5-AG with 2-hour glucose and fasting glucose. We constructed non-parametric ROC curves by multiplying 1,5-AG values by -1 since 1,5-AG is inversely associated with hyperglycemia.

We then further investigated the true negative, false positive, false negative, true positive groups using multinomial logistic regression to assess predictors of those categories, with true negative as the reference, adjusting for age, sex, and race-center. The predictors we examined were age, sex, race-center, body mass index, total cholesterol, triglycerides, HDL, hypertension, eGFR, ACR (log transformed), dairy intake (tertiles), and bread and/or rice intake (tertiles). We also examined scatterplots and Spearman's and Pearson's correlations of 1,5-AG and the dietary intake variables.

Sensitivity and Secondary Analyses

Because concerns have been raised regarding the reliability of 1,5-AG in the setting of chronic kidney disease[23,24] and liver disease,[25] we conducted sensitivity analyses excluding these individuals. We excluded participants with G3b, G4, or G5 chronic kidney disease (n=75) and in a separate analysis excluded participants with elevated liver enzymes (ALT>38.1 U/L or AST>44.4 U/L; n=225; **Figure D-1**). We evaluated the diagnostic performance of 1,5-AG relative to categories of hyperglycemia

and reported sensitivity, specificity, positive and negative likelihood ratios, and positive and negative predictive values and ROC curves in each subgroup.

In a secondary analysis, we compared 1,5-AG measured at Visit 2 to hyperglycemia defined by elevated HbA1c, elevated fasting glucose, and the combination of elevated HbA1c and fasting glucose (as the gold standards) from the second study visit (n=11,582; **Figure D-1**; HbA1c was only available at the second ARIC visit).

Statistical analyses were conducted in Stata 15.1 (StataCorp, College Station, TX). The Venn diagram was created using RStudio (RStudio, Inc., Boston, MA) Eulerr Package[26].

Results

The 7,813 study participants ranged in age from 52-75 years; 57% were female, and 16% black. 1,5-AG, 2-hour glucose, and fasting glucose had means (SD) of 20.6 (6.85) µg/mL, 137 (52.2) mg/dL, and 102 (17.5) mg/dL, respectively. In all, 818 (10.5%) participants had 2-hour glucose ≥200 mg/dL, 398 (5.1%) participants had fasting glucose ≥126 mg/dL, and 435 (5.6%) participants had 1,5-AG <10 µg/mL.

1,5-AG <10 µg/mL was associated with traditional diabetes risk factors; those with low concentrations were more likely to be black and have parental history of diabetes, have higher fasting glucose and 2-hour glucose concentrations, higher triglycerides, and reduced kidney function and more likely to have kidney damage than their counterparts with 1,5-AG ≥10 µg/mL (**Table 1**). However, there were no significant differences in body mass index (p=0.27) or hypertension (p=0.26) comparing individuals with 1,5-AG <10 µg/mL vs. ≥10 µg/mL. 2-hour glucose ≥200 mg/dL and fasting glucose

≥126 mg/dL were associated with traditional diabetes risk factors, including body mass index and hypertension (**Table 1**).

The overall prevalence of elevated 2-hour glucose, or elevated fasting glucose, or low 1,5-AG (<10 μg/mL) was 15.0%, with the remaining 85.0% of participants classified as true negatives (**Figure 1**). 2.1% (n=164) of participants had hyperglycemia (defined by 2-hour glucose or fasting glucose) and 1,5-AG <10 μg/mL (true positives). It was rare for participants to have elevated fasting glucose and 1,5-AG <10 μg/mL but not elevated 2-hour glucose (0.1%, n=5). 3.5% of participants (n=271) had isolated 1,5-AG <10 μg/mL, meaning over half of participants with 1,5-AG <10 μg/mL (271/435) did not have hyperglycemia (false positives). 9.4% of participants (n=738) had hyperglycemia (defined by 2-hour glucose or fasting glucose), but did not have 1,5-AG <10 μg/mL (false negatives).

The 1.5% (n=120) of participants identified by all three biomarkers (2-hour, fasting, and 1,5-AG) had a mean (SD) 2-hour glucose of 322 (84.0) mg/dL and a fasting glucose of 184 (57.8) mg/dL. Whereas, the 2.5% of participants (n=194) identified by elevated 2-hour glucose and fasting glucose, but not 1,5-AG, had mean (SD) 2-hour glucose 261 (39.5) mg/dL and fasting glucose 145 (17.5) mg/dL.

When assessing the performance of 1,5-AG to identify hyperglycemia, we found that regardless of the cut-point used, 1,5-AG tended to be highly specific but insensitive for the identification of hyperglycemia (**Table 2**). Overall, 1,5-AG had high negative predictive values for identifying hyperglycemia.

Scatterplots assessing the continuous associations of 1,5-AG with fasting and 2-hour glucose demonstrated moderate correlations, but only at low concentrations of 1,5-

AG (e.g., below 10 μg/mL); at higher concentrations of 1,5-AG, the variables were essentially uncorrelated (**Figure D-2**).

The area under the ROC curve comparing 1,5-AG continuously to 2-hour glucose ≥200 mg/dL was 0.66 (95% CI 0.64, 0.68). Conducting the same analysis but comparing 1,5-AG to fasting glucose ≥126 mg/dL, and both 2-hour glucose ≥200 mg/dL and fasting glucose ≥126 mg/dL the resulting areas under the ROCs were 0.72 (95% CI 0.69, 0.75), and 0.78 (95% CI 0.75, 0.81), respectively (**Figure 2**). By way of comparison, the ROC curve for fasting glucose compared to 2-hour glucose ≥200 mg/dL was 0.84 (95% CI 0.82, 0.86) and for 2-hour glucose compared to fasting glucose ≥126 mg/dL was 0.94 (95% CI 0.92, 0.95).

Compared to true negatives (no hyperglycemia and 1,5-AG ≥10 μg/mL), false positives (1,5-AG <10 μg/mL with normal 2-hour glucose and fasting glucose) were older, more likely to be black, had lower eGFR, and had higher ACR (**Table 3**). False negatives were older, had higher body mass index, triglycerides, and ACR, had lower HDL, and were more likely to have hypertension compared to true negatives (**Table 3**). Interestingly, there were no dietary correlates of false positive 1-5 AG, although a high-bread and rice diet showed suggestion of association with higher 1-5AG and high-intake of dairy products showed suggestion of association with lower 1,5-AG (**Figure D-3**).

Regardless or whether we excluded the small number of participants with G3b, G4, or G5 chronic kidney disease (n=75) or elevated liver enzymes (n=225) performance of 1,5-AG to identify hyperglycemia remained largely unchanged (**Table D-2 and Table D-3**).

Among the 11,582 eligible participants without diagnosed diabetes who attended Visit 2 (6 years earlier), 4.1% had HbA1c ≥6.5% and 6.5% had 1,5-AG <10 μg/mL. 1,5-AG had high specificity but low sensitivity for the identification of hyperglycemia defined by HbA1c in Visit 2 measurements (**Table D-4**). The areas under the ROC curves for 1,5-AG compared to HbA1c ≥6.5%, elevated fasting glucose, or both elevated HbA1c and elevated fasting glucose were 0.74 (95% CI, 0.71, 0.77), 0.67 (95% CI, 0.64, 0.69), and 0.80 (95% CI, 0.77, 0.83), respectively.

Discussion

In this community-based population of persons with no history of diabetes, 1,5-AG was not highly concordant with 2-hour glucose. 1,5-AG demonstrated high specificity but low sensitivity to identify hyperglycemia in a community-based setting. Generally, the test characteristics of 1,5-AG suggest it has limited utility for diabetes screening in the general U.S. population.

Interestingly, despite that 1,5-AG demonstrated high specificity as a marker of hyperglycemia, the risk factor relationships for low 1,5-AG were not as strong compared to other definitions of hyperglycemia in this population. However, the specificity of 1,5-AG also suggests that it is capturing a small number of potentially high-risk individuals experiencing glycemic excursions. This was demonstrated by the fact that the mean 2-hour glucose and fasting glucose among participants identified by all three biomarker cut-points was higher than those identified by the two glucose measures alone.

Prior studies of the performance of 1,5-AG to identify hyperglycemia have been conflicting as to the utility of 1,5-AG for screening[10–12,27]. The reasons for the differences in results of prior studies in persons without diagnosed diabetes may relate to the

characteristics of the study populations, differences in the method of measurement of 1,5-AG, and/or chance variation given the small sample sizes of prior studies.

There may be important non-glycemic factors that influence 1,5-AG outside of the setting of overt diabetes, which could help explain its lack of concordance with traditional glucose tests.

Population characteristics in particular may contribute to the heterogeneity in the determinants of 1,5-AG among those without diagnosed diabetes. Dietary factors, for instance, differ across populations and may be important. Our recent work, along with the contributions of others, suggests that diet may directly affect 1,5-AG concentrations, particularly outside the setting of overt diabetes[28,29]. Different foods have varying amounts of 1,5-AG[30,31]. Soybeans have particularly high 1,5-AG content, followed by modest amounts in foods like bread and rice, and very small amounts in dairy products[30]. It is possible that the varying quantities of these foods across populations could influence 1,5-AG and its performance as a measure of hyperglycemia, particularly in predominately non-diabetic populations. While we did not observe dietary factors as driving forces of the false positive group, the correlations were in the expected directions and our capacity to assess these relationships was limited. Additional controlled studies are needed to understand the influence of diet on 1,5-AG, particularly outside of the setting of diagnosed diabetes.

Previous genetic analyses have suggested that there may be differences in 1,5-AG due to variants that influence glucose metabolism[32]. Prevalence of kidney and liver disease may also be relevant. Other investigators have suggested the reliability of 1,5-AG may be uncertain in setting of kidney disease given its renal handling and one study

observed concentrations may also be altered in the setting of liver disease[25,27,33]. False positives in our data were more likely to have reduced kidney function and increased kidney damage. Nonetheless, our results were similar after excluding the small numbers of individuals with chronic kidney disease, impaired kidney function, or elevated liver enzymes. All of these factors taken together suggest that there is heterogeneity in the means to obtain low 1,5-AG outside of glycemic excursions, like diet, genetics, reduced kidney function, increased kidney damage, and liver disease, which could help explain its lack of concordance with traditional glucose tests.

Our analysis has some limitations to consider in the context of these results. This study was conducted in a population with a low prevalence of hyperglycemia. We also only had single measures of 2-hour glucose and fasting glucose to define states of hyperglycemia. Two-hour glucose and fasting glucose were both measured in 1996-98, while 1,5-AG was measured in stored samples in 2015-16. Technological differences or differences due to long-term storage could have decreased the concordance of the measures. In our assessment of factors related to those with false positive results, we did not have concurrently available dietary data. While we would expect dietary habits to be relatively stable over time, it is possible that there were changes over the three-year gap in measurements. Self-reported dietary data is notoriously problematic, which may have led to misclassification and underestimation of any true relationship with 1,5-AG. Additionally, while not our primary aim, HbA1c, a biomarker routinely used for diagnosis of diabetes, was not available at the contemporaneous study visit with 2-hour glucose. We performed a secondary analysis comparing 1,5-AG and HbA1c at the second study visit to help address this concern.

There were also several strengths to our approach. Our primary strength was the large, racially diverse community-based U.S. population of relevant age for diabetes screening. All measurements in ARIC were conducted by trained staff using standardized protocols. We were able to compare 1,5-AG to multiple measures of hyperglycemia (2-hour glucose, fasting glucose and HbA1c).

Comparing 1,5-AG and 2-hour glucose allowed us to assess the concordance between two markers that reflect postprandial hyperglycemia. Our results are consistent with our understanding of the biology of 1,5-AG as indicating substantial glycemic excursions (glucose concentrations exceeding the renal threshold). Fasting glucose concentrations of >160 mg/dL were rare in the present population (n=95, 1.2%). We also observed that there might be several reasons people have low 1,5-AG values outside of the setting of diabetes, which require further investigation. Our results suggest that people identified by 1,5-AG in addition to the traditional definitions (2-hour glucose, fasting glucose) are a very high-risk population. In conclusion, 1,5-AG is a specific biomarker for hyperglycemic excursions, but may have limited utility for diabetes screening in the general population.

Table 1. Participant characteristics according to elevated 2-hour glucose and/or elevated fasting glucose and low 1,5-AG (<10 µg/mL), the ARIC Study (1996-1998), n=7,813*

	2-hour glucose			Fasting glucose			1,5-AG		
	<200 mg/dL n=6,995	≥200 mg/dL n=818	*p*-value†	<126 mg/dL n=7,415	≥126 mg/dL n=398	*p*-value	≥10 µg/mL n=7,378	<10 µg/mL n=435	*p*-value
Age (years)	63.0 (5.6)	64.8 (5.6)	<0.001	63.2 (5.6)	63.6 (5.5)	0.15	63.2 (5.6)	64.1 (5.9)	<0.001
Female, %	56.4	62.1	0.002	57.3	50.0	0.004	56.9	57.9	0.67
Race-center, %									
Washington County, MD-White	27.0	32.8		27.4	31.4		27.8	23.9	
Minneapolis, MN-White	33.2	26.9	0.001	32.8	26.6	0.004	32.6	31.5	0.014
Forsyth County, NC-White	23.7	23.8		23.9	20.6		23.8	23.0	
Forsyth County, NC-Black	1.9	2.1		1.9	2.5		1.9	1.8	
Jackson, MS-Black	14.2	14.4		14.0	18.8		13.9	19.8	
Body mass index (kg/m^2)	28.2 (5.3)	30.2 (5.6)	<0.001	28.3 (5.3)	31.8 (5.9)	<0.001	28.4 (5.4)	28.7 (5.4)	0.27
Obese, %	30.5	47.6	<0.001	31.0	56.8	<0.001	32.0	36.3	0.063
Waist-to-hip ratio	0.9 (0.1)	1.0 (0.1)	<0.001	0.9 (0.1)	1.0 (0.1)	<0.001	0.9 (0.1)	1.0 (0.1)	0.068
Fasting glucose (mg/dL)	98.7 (9.6)	127.4 (37.6)	<0.001	98.9 (9.3)	153.7 (39.8)	<0.001	100.4 (12.5)	123.4 (49.1)	<0.001
2-hour glucose (mg/dL)	124.2 (33.3)	247.7 (53.5)	<0.001	130.6 (41.2)	258.4 (79.3)	<0.001	134.0 (45.9)	190.1 (101)	<0.001
1,5-AG (µg/mL)	20.5 (6.1)	16.5 (7.2)	<0.001	20.4 (6.1)	14.5 (7.9)	<0.001	20.8 (5.6)	6.9 (2.5)	<0.001
Total cholesterol (mg/dL)	201.5 (36.0)	203.4 (38.2)	0.17	201.6 (35.7)	204.3 (44.8)	0.14	201.8 (36.2)	200.2 (37.0)	0.36
HDL cholesterol (mg/dL)	51.2 (16.5)	45.4 (14.8)	<0.001	51.1 (16.5)	41.3 (13.0)	<0.001	50.7 (16.4)	49.0 (17.4)	0.033
Triglycerides (mg/dL)	136.1 (76.4)	182.3 (107)	<0.001	138.0 (77.1)	195.9 (126)	<0.001	140.1 (79.9)	154.1 (102)	<0.001

Data are means (SD) unless otherwise noted

* Variables with missingness (variable, n): body mass index, 11; obese, 11; waist-to-hip ratio, 8; hypertension, 29; education level, 11; smoking status, 10; drinking status, 9; ACR stage, 55

† *p*-value for global test: *t*-test for continuous variables and Pearson's chi-squared tests for categorical variables

Abbreviations: HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; ACR, albumin-creatinine-ratio

Table 1., continued

	2-hour glucose			Fasting glucose			1,5-AG		
	<200 mg/dL n=6,995	≥200 mg/dL n=818	*p*-value†	<126 mg/dL n=7,415	≥126 mg/dL n=398	*p*-value	≥10 µg/mL n=7,378	<10 µg/mL n=435	*p*-value
Hypertension, %	41.4	62.3	<0.001	42.6	62.5	<0.001	43.4	46.2	0.26
Less than high school, %	15.4	20.6	<0.001	15.7	21.7	0.001	15.9	17.1	0.52
Current smoker, %	13.9	11.4	0.042	13.7	11.8	0.28	13.8	11.3	0.14
Current drinker, %	54.6	47.2	<0.001	54.0	49.5	0.079	53.8	53.3	0.85
Parental history of diabetes, %	21.2	30.4	<0.001	21.6	33.4	<0.001	21.8	28.0	0.002
eGFR <60 (mL/min/1.73m^2), %	5.5	6.5	0.25	5.5	6.3	0.52	5.4	8.5	0.006
ACR Stage (ug/mg), %									
≥30 & ≤300	4.2	7.6	<0.001	4.3	10.7	<0.001	4.3	10.0	<0.001
>300	0.6	2.0		0.6	2.3		0.7	0.9	

Data are means (SD) unless otherwise noted

* Variables with missingness (variable, n): body mass index, 11; obese, 11; waist-to-hip ratio, 8; hypertension, 29; education level, 11; smoking status, 10; drinking status, 9; ACR stage, 55

† *p*-value for global test: *t*-test for continuous variables and Pearson's chi-squared tests for categorical variables

Abbreviations: HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; ACR, albumin-creatinine-ratio

Figure 1. Distribution of participants according to clinical cut-points of elevated 2-hour glucose and/or elevated fasting glucose, and low 1,5-AG (<10 µg/mL), n=7,813

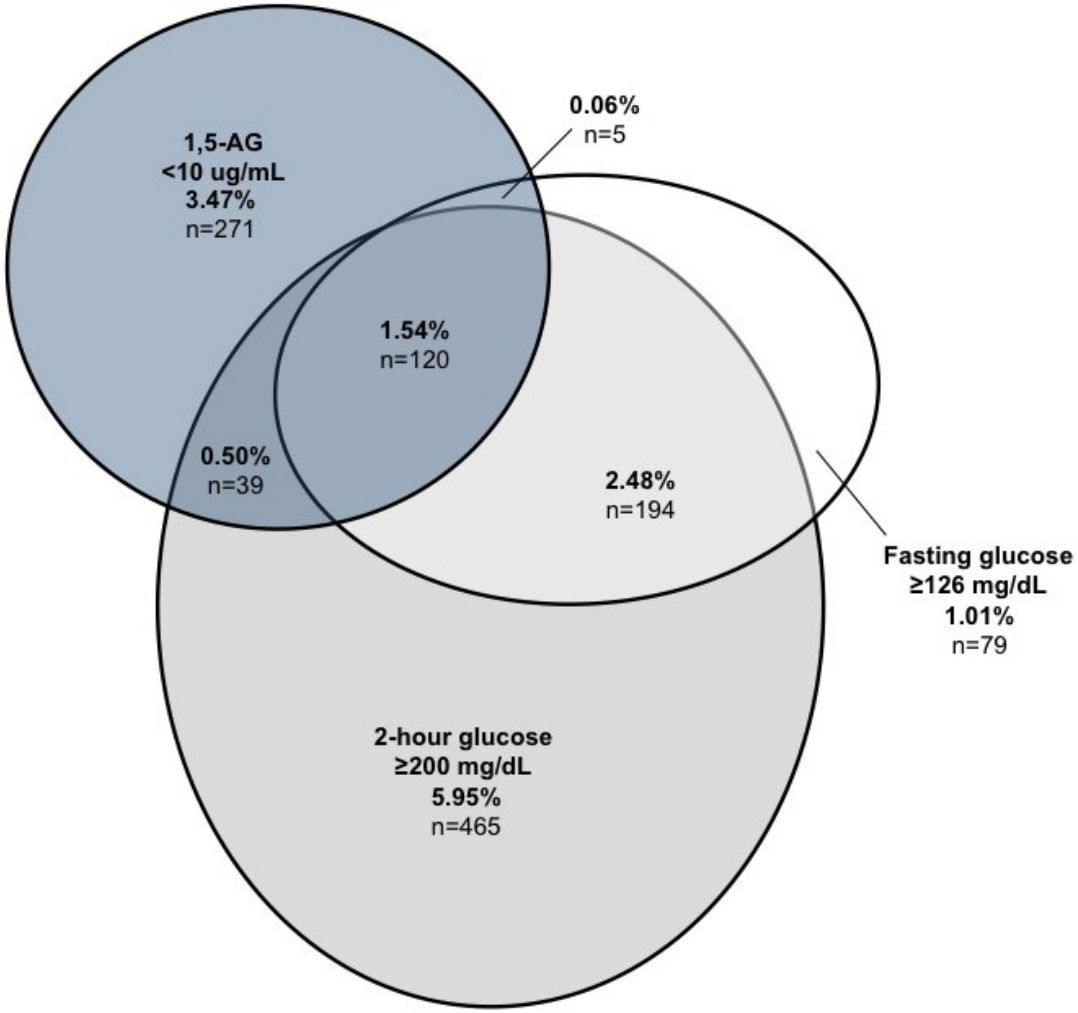
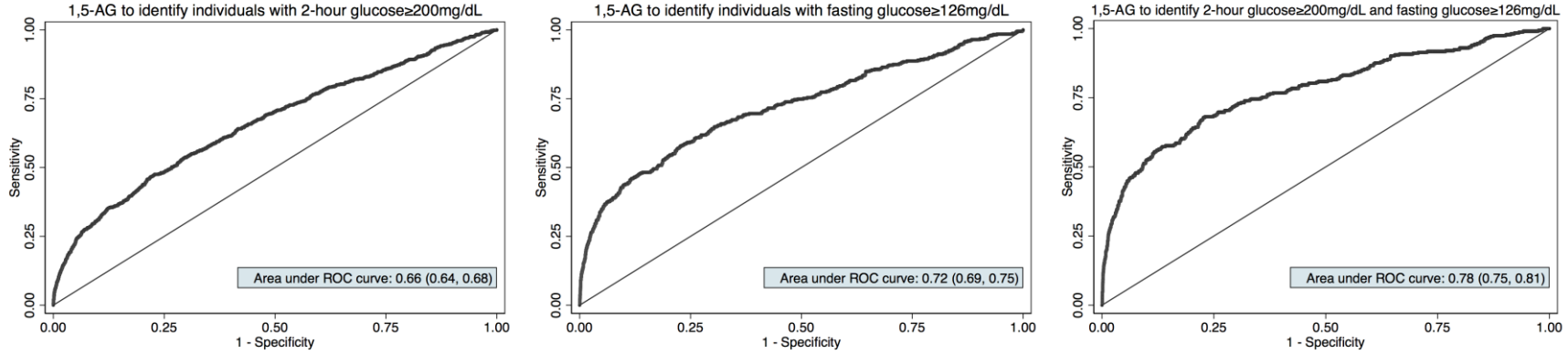


Table 2. Diagnostic performance of 1,5-AG to identify elevated 2-hour glucose and/or fasting glucose, n=7,813

1,5-AG cut point	Sensitivity	Specificity	+Likelihood Ratio	-Likelihood Ratio	Positive predictive value	Negative predictive value
1,5-anhydroglucitol compared to 2-hour glucose ≥200 mg/dL (n=818)						
<10 µg/mL	19.4%	96.1%	4.93	0.84	36.6%	91.1%
(n = 435)	(16.8, 22.3)	(95.6, 96.5)	(4.11, 5.90)	(0.81, 0.87)	(32.0, 41.3)	(90.4, 91.7)
<12 µg/mL	27.6%	92.6%	3.75	0.78	30.5%	91.6%
(n = 741)	(24.6, 30.8)	(92.0, 93.2)	(3.27, 4.31)	(0.75, 0.82)	(27.2, 34.0)	(91.0, 92.3)
<16 µg/mL	46.7%	77.9%	2.11	0.68	19.8%	92.6%
(n=1,928)	(43.2, 50.2)	(76.9, 78.9)	(1.94, 2.30)	(0.64, 0.73)	(18.1, 21.7)	(91.9, 93.2)
1,5-anhydroglucitol compared to fasting glucose ≥126 mg/dL (n=398)						
<10 µg/mL	31.4%	95.8%	7.51	0.72	28.7%	96.3%
(n = 435)	(26.9, 36.2)	(95.3, 96.3)	(6.27, 9.01)	(0.67, 0.77)	(24.5, 33.2)	(95.8, 96.7)
<12 µg/mL	38.9%	92.1%	4.93	0.66	20.9%	96.6%
(n = 741)	(34.1, 43.9)	(91.5, 92.7)	(4.26, 5.70)	(0.61, 0.72)	(18.0, 24.0)	(96.1, 97.0)
<16 µg/mL	57.8%	77.1%	2.52	0.55	11.9%	97.1%
(n=1,928)	(52.8, 62.7)	(76.1, 78.1)	(2.30, 2.77)	(0.49, 0.62)	(10.5, 13.5)	(96.7, 97.6)
1,5-anhydroglucitol compared to 2-hour glucose ≥200 mg/dL and fasting glucose ≥126 mg/dL (n=314)						
<10 µg/mL	38.2%	95.8%	9.10	0.65	27.6%	97.4%
(n = 435)	(32.8, 43.8)	(95.3 96.2)	(7.62, 10.9)	(0.59, 0.70)	(23.4, 32.0)	(97.0, 97.7)
<12 µg/mL	47.8%	92.1%	6.06	0.57	20.2%	97.7%
(n = 741)	(42.1, 53.5)	(91.5, 92.7)	(5.27, 6.97)	(0.51, 0.63)	(17.4, 23.3)	(97.3, 98.0)
<16 µg/mL	67.8%	77.1%	2.97	0.42	11.0%	98.3%
(n=1,928)	(62.4, 73.0)	(76.2, 78.1)	(2.72, 3.23)	(0.36, 0.49)	(9.68, 12.5)	(97.9, 98.6)

Figure 2. Receiver operator characteristic (ROC) curve of 1,5-AG for detection of elevated 2-hour glucose and/or elevated fasting glucose



Abbreviations: ROC, receiver operating characteristic

Table 3. Adjusted OR (95% CI) to assess predictors of discordance of true negative, false positive, false negative, and true positive results, n=7,813

	Adjusted* OR (95% CI)			
	True Negative 2-hour <200 mg/dL, fasting glucose <126 mg/dL, and 1,5-AG ≥10 µg/mL n=6,371	**False Positive** 2-hour <200 mg/dL, fasting glucose <126 mg/dL, and 1,5-AG <10 µg/mL n=262	**False Negative** 2-hour ≥200 mg/dL and/or fasting glucose ≥126 mg/dL, and 1,5-AG ≥10 µg/mL n=712	**True Positive** 2-hour ≥200 mg/dL and/or fasting glucose ≥126 mg/dL, and 1,5-AG <10 µg/mL n=158
Age (years)	1 (REF)	**1.23** (1.10, 1.37)	**1.33** (1.24, 1.42)	**1.18** (1.03, 1.36)
Female (male, ref)	1 (REF)	1.22 (0.95, 1.56)	**1.28** (1.09, 1.50)	0.86 (0.63, 1.17)
Race-center (Minneapolis, MN-white, ref)				
Jackson, MS-black	1 (REF)	**1.70** (1.21, 2.41)	**1.35** (1.05, 1.74)	1.35 (0.84, 2.15)
Washington County, MD-white	1 (REF)	0.83 (0.59, 1.16)	**1.52** (1.24, 1.86)	1.04 (0.70, 1.56)
Forsyth County, NC-black	1 (REF)	1.02 (0.41, 2.57)	1.50 (0.88, 2.55)	1.01 (0.31, 3.30)
Forsyth County, NC-white	1 (REF)	1.08 (0.77, 1.50)	**1.26** (1.02, 1.57)	0.89 (0.57, 1.37)
Body mass index (kg/m^2)	1 (REF)	0.88 (0.77, 0.99)	**1.40** (1.31, 1.50)	**1.45** (1.28, 1.65)
Total cholesterol (mg/dL)	1 (REF)	0.98 (0.97, 1.00)	1.01 (0.99, 1.02)	1.01 (0.99, 1.03)
Triglycerides (mg/dL)	1 (REF)	0.99 (0.98, 1.00)	**1.03** (1.02, 1.03)	**1.03** (1.03, 1.04)
HDL (mg/dL)	1 (REF)	1.02 (0.98, 1.06)	**0.85** (0.83, 0.88)	**0.76** (0.70, 0.81)
Hypertension (no, ref)	1 (REF)	0.90 (0.69, 1.16)	**2.33** (1.98, 2.74)	**1.50** (1.09, 2.07)
eGFR ($mL/min/1.73\ m^2$)	1 (REF)	**0.96** (0.92, 1.00)	1.03 (1.00, 1.06)	1.04 (0.98, 1.10)
Log ACR (ug/mg)	1 (REF)	**2.01** (1.26, 3.20)	**1.78 (**1.30, 2.39)	**4.41** (2.59, 7.49)

Bold indicates $p < 0.05$

* Adjusted for age, sex, race-center; continuous variables are scaled per 5 units

* Variables with missingness (variable, n): body mass index, 11; hypertension, 29; log ACR, 55; dairy intake, 216; bread and/or rice intake, 208

Abbreviations: OR, odds ratio; 1,5-AG, 1,5-anhydroglucitol; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate; ACR, albumin-creatinine-ratio

Table 3., continued

	Adjusted* OR (95% CI)			
	True Negative 2-hour <200 mg/dL, fasting glucose <126 mg/dL, and 1,5-AG ≥10 µg/mL n=6,371	**False Positive** 2-hour <200 mg/dL, fasting glucose <126 mg/dL, and 1,5-AG <10 µg/mL n=262	**False Negative** 2-hour ≥200 mg/dL and/or fasting glucose ≥126 mg/dL, and 1,5-AG ≥10 µg/mL n=712	**True Positive** 2-hour ≥200 mg/dL and/or fasting glucose ≥126 mg/dL, and 1,5-AG <10 µg/mL n=158
Dairy intake (lowest tertile, ref)	1 (REF)			
Middle tertile	1 (REF)	1.04 (0.76, 1.42)	1.03 (0.85, 1.25)	0.86 (0.58, 1.28)
Highest tertile	1 (REF)	1.13 (0.83, 1.54)	1.15 (0.95, 1.39)	1.02 (0.69, 1.50)
Bread and rice intake (lowest tertile, ref)	1 (REF)			
Middle tertile	1 (REF)	0.94 (0.70, 1.27)	1.07 (0.88, 1.29)	1.05 (0.71, 1.57)
Highest tertile	1 (REF)	0.83 (0.61, 1.13)	1.03 (0.85, 1.25)	1.29 (0.87, 1.90)

Bold indicates $p < 0.05$

* Adjusted for age, sex, race-center; continuous variables are scaled per 5 units

* Variables with missingness (variable, n): body mass index, 11; hypertension, 29; log ACR, 55; dairy intake, 216; bread and/or rice intake, 208

Abbreviations: OR, odds ratio; 1,5-AG, 1,5-anhydroglucitol; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate; ACR, albumin-creatinine-ratio

Chapter 4. Associations of 1,5-anhydroglucitol and 2-hour glucose with major clinical outcomes in the Atherosclerosis Risk in Communities Study

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Abstract

Objectives. 1,5-anhydroglucitol (1,5-AG) is a novel biomarker of glycemic control that has been proposed to monitor recent hyperglycemic excursions in persons with diabetes. The clinical utility of 1,5-AG outside of the setting of diagnosed diabetes is unclear, but it is possible that it may identify people at high risk for diabetes and its complications. The objective of this study was to compare the associations of 1,5-AG with 2-hour glucose for risk of major clinical complications.

Research Design and Methods. We conducted a prospective analysis of 6,644 Atherosclerosis Risk in Communities (ARIC) Study participants without diagnosed diabetes followed for nearly 20 years for incident diagnosed diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality. All participants were disease-free at baseline. We assessed associations of 1,5-AG and 2-hour glucose (modeled categorically and continuously with restricted cubic splines) with adverse outcomes using Cox models with evaluated improvement in risk discrimination using the c-statistic.

Results. 1,5-AG <10 μg/mL was statistically significantly associated with incident diabetes (HR: 2.70, 95% CI 2.31, 3.15), and showed suggestion of association with incident chronic kidney disease, cardiovascular disease, and all-cause mortality compared to 1,5-AG ≥10 μg/mL. Continuous associations of 1,5-AG with outcomes displayed a

clear threshold effect, with risk associations generally observed only in the 1,5-AG <10 μg/mL group. Comparing associations of 1,5-AG and 2-hour glucose with outcomes resulted in larger c-statistics for 2-hour glucose than 1,5-AG for all outcomes (difference in c-statistic [2-hour glucose-1,5-AG] for diagnosed diabetes: 0.17 [95%CI, 0.15, 0.19]; chronic kidney disease 0.02 [95%CI 0.00, 0.05]; cardiovascular disease 0.03 [95%CI, 0.00, 0.06]; and all-cause mortality 0.04 [95%CI, 0.02, 0.06]). 1,5-AG did also not improve risk stratification when added to models with traditional glucose measures (fasting or 2-hour glucose).

Conclusions. In this community-based population without diagnosed diabetes, low 1,5-AG was modestly associated with major clinical outcomes and did not outperform 2-hour glucose. Further research is needed to determine the utility of 1,5-AG outside of the setting of diagnosed diabetes.

Introduction

Diabetes poses a substantial burden on patients, providers, and the health care system[1]. Persons with diabetes are at increased risk for microvascular and macrovascular disease and at high risk of death[2]. There is widespread screening for diabetes in the U.S., with the aim of identifying and intervening early in the disease process to prevent major complications. Routine measurement of biomarkers of hyperglycemia is used to screen and diagnose diabetes[3] and identify those at increased risk for its associated outcomes.

Glucose measured after the administration a 75-g oral glucose load (simulated carbohydrate-rich meal) is a well-established test used to diagnose diabetes. In the setting of insulin resistance and/or impaired insulin secretion, blood glucose concentrations will remain elevated (≥200 mg/dL) two hours following the oral glucose load. 1,5-

Anhydroglucitol (1,5-AG) is a less common measure of hyperglycemia that reflects glycemic excursions, although through a different mechanism. 1,5-AG is a monosaccharide that remains stable in blood at normal levels of glycemia. However, when circulating plasma glucose exceeds the renal threshold for glucose reabsorption (~160-180 mg/dL), 1,5-AG and glucose compete for reabsorption in the renal proximal tubule, resulting in increased excretion of 1,5-AG in the urine and lower 1,5-AG concentrations in the blood. 1,5-AG is attractive as an alternative measure of hyperglycemia as it is a non-fasting test, does not involve administration of a carbohydrate challenge, and can be measured in a single blood sample. Some investigators have suggested the utility of 1,5-AG for diabetes screening[4–6].

Elevated 2-hour glucose and low 1,5-AG concentrations are both associated with future outcomes including microvascular and macrovascular events, and all-cause mortality[7–11]. However, prior studies have not compared associations of 2-hour glucose to 1,5-AG in the same study population. We therefore evaluated and compared the associations of 1,5-AG and 2-hour glucose with risk for future diagnosed diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality in adults in the Atherosclerosis Risk in Communities (ARIC) Study, a U.S-based prospective cohort.

Methods

Study Population

The ARIC Study was initiated in 1987, enrolling 15,792 participants from four communities (Washington County, Maryland; Minneapolis, Minnesota; Jackson, Mississippi; and Forsyth County, North Carolina) in the first study visit[12]. Since the baseline visit (Visit 1), there have been six subsequent completed or ongoing visits (Visit

2: 1990-92, Visit 3:1993-95, Visit 4:1996-98, Visit 5: 2011-13, Visit 6: 2016-17, and Visit 7: 2018-19). Investigators obtained study approvals from institutional review boards and written informed consent from all participants.

Our study population included the 11,656 participants who attended the fourth visit (1996-98) when both 1,5-AG and 2-hour glucose were measured. We then excluded participants ineligible for the oral glucose tolerance test or missing glycemic markers (n=3,587), those with prevalent diagnosed diabetes, chronic kidney disease, or cardiovascular disease (n=1,299), those who were not black or white or who were black from the Washington Country or Minneapolis sites (n=43), and those missing covariates of interest (n=81; see **Figure E-1** for more details). We followed the resulting 6,644 participants over ~20 years for incident disease, including diagnosed diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality.

Exposure Measurements

1,5-AG, 2-hour glucose, and fasting glucose were measured in plasma at the Baylor College of Medicine. 1,5-AG was measured using the GlycoMark assay in 2015-2016 in stored samples obtained from ARIC participants at the fourth study visit (inter-assay CV, 4.54%). Blood samples were collected in the fasting state and 2-hours following administration of 75-g glucose load among those without diagnosed diabetes or currently taking medications for diabetes at the study visit. The oral glucose tolerance test protocol also excluded participants who had prior stomach or intestinal surgery, those on dialysis, those who were fasting for less than 10 hours[13] (see **Figure E-1** for detail). Glucose was measured in plasma using the hexokinase method with the Roche Hitachi 911 automated chemistry analyzer (or autoanalyzer). For categorical analyses of these

biomarkers, we used the following cut points: 1,5-AG ≥10 μg/mL, <10μg/mL; 2-hour glucose < 200 mg/dL, ≥200 mg/dL; and fasting glucose <126 mg/dL, ≥126 mg/dL.

We previously evaluated the cross-sectional concordance of 1,5-AG, 2-hour glucose, and fasting glucose and found substantial discordance across these measures[14]. To assess the clinical implications of this discordance, we cross-tabulated categories of 1,5-AG with clinical categories of 2-hour glucose and fasting glucose and compared those identified as "true negatives" (TN), "false positives" (FP), "false negatives" (FN), and "true positives" (TP). That is, we defined a TN as those without hyperglycemia (2-hour <200 mg/dL and fasting glucose <126 mg/dL) and 1,5-AG ≥10 μg/mL. We defined a FP as those without hyperglycemia (2-hour <200 mg/dL and fasting glucose <126 mg/dL) and 1,5-AG <10 μg/mL. We defined a FN as those with hyperglycemia (2-hour ≥200 mg/dL and/or fasting glucose ≥126 mg/dL) and 1,5-AG ≥10 μg/mL. Finally, we defined a TP as those with hyperglycemia (2-hour ≥200 mg/dL and/or fasting glucose ≥126 mg/dL) and 1,5-AG <10 μg/mL.

Assessment of Outcomes

We followed participants prospectively from baseline (Visit 4; 1996-98) for incident diabetes and major clinical outcomes (incident chronic kidney disease, cardiovascular disease, and all-cause mortality) for nearly 20 years (end of follow-up: December 31, 2013 for chronic kidney disease; December 31, 2015 for all other outcomes). We defined incident diabetes as self-report of physician diagnosis or glucose-lowering medication use during a study visit or annual or semi-annual telephone call;[15] chronic kidney disease as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (from CKD-EPI equation[16] using creatinine) at Visit 5 (2011-13) and a decline from

Visit 4 of at least 25%, a chronic kidney disease-related hospitalization or death[17], or end stage renal disease event identified by linkage to the United States Renal Data System; cardiovascular disease as an adjudicated hospitalization or death from coronary heart disease or ischemic stroke[12]; and all-cause mortality as identified from surveillance of all ARIC participants.

Covariate Measurement

Participants reported demographic characteristics (age, sex, race, parental history of diabetes, and education level) at cohort initiation (Visit 1). Because race may be confounded by study center[12], we defined race-center as Washington County, Maryland-White; Minneapolis, Minneapolis-White; Forsyth County, North Carolina-White; Forsyth County, North Carolina-Black; Jackson, Mississippi-Black.

Other covariates were measured at baseline of the present study (Visit 4). Height, weight, waist-to-hip ratio, total cholesterol, HDL cholesterol, and triglycerides were measured using standard anthropometric and phlebotomy protocols[18,19]. Body mass index was calculated from weight and height (kg/m^2). Mean systolic and diastolic blood pressure were calculated by averaging two measurements[20]. We defined hypertension as self-report of hypertensive medications, mean systolic blood pressure ≥140 mmHg, or mean diastolic blood pressure ≥90mmHg. Participants self-reported whether they were currently, formerly, or never smokers and/or drinkers[18]. $eGFR_{cr}$ was calculated from creatinine using the CKD-EPI equation[16]. We derived albumin-to-creatinine ratio from albumin and creatinine measurements in urine samples[21].

Statistical analysis

We compared participants' baseline characteristics by categories generated from

the cross-tabulation of 1,5-AG with clinical categories of 2-hour glucose and fasting glucose (TN, FP, FN, TP). We used Cox proportional hazards models to characterize associations with incident outcomes, using categories of each biomarker (1,5-AG ≥10 μg/mL, <10μg/mL; 2-hour glucose < 200 mg/dL, ≥200 mg/dL; and fasting glucose <126 mg/dL, ≥126 mg/dL) and using restricted cubic splines with four knots located at the 5^{th}, 35^{th}, 65^{th}, and 95^{th} percentiles to more flexibly model each of the biomarkers. We graphed the continuous associations of 1,5-AG, 2-hour glucose, and fasting glucose with incident diagnosed diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality and compared the prognostic value of the associations by calculating differences in Harrell's C-statistic.

We also evaluated the associations of the categories generated from the cross-tabulation of 1,5-AG with clinical categories of 2-hour glucose and fasting glucose (TN, FP, FN, TP) with risk of future diagnosed diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality, using TN as the reference. To assess whether 1,5-AG helped further risk stratify those in addition to 2-hour glucose and/or fasting glucose, we again used Harrell's c-statistic to compare continuous spline models.

We primarily present unadjusted results given the importance in understanding the comparative overall (crude) associations, which would be most relevant for informing diabetes screening. We also conducted two supplementary analyses evaluating the associations after adjustment for potential confounding variables. In these analyses, Model 1 included age, sex, race-center and Model 2 included all variables in Model 1 plus body mass index, systolic blood pressure, hypertension medication use (no, yes), total cholesterol, HDL, triglycerides, education (less than high school, high

school/vocational school, college or higher), smoking status (current, former, never), drinking status (current, former, never), parental history of diabetes (no, yes), $eGFR_{cr}$, and log transformed albumin-to-creatinine ratio). For all of our analyses, we used Stata 15.1 (StataCorp, College Station, TX).

Results

At baseline, participants were a mean of 63 years old, 60% female, and 17% black. Mean (SD) 2-hour glucose, fasting glucose, and 1,5-AG were 136 (51.8) mg/dL, 101 (17.7) mg/dL, and 20.0 (6.2) µg/mL. Overall, 86% of participants were classified as TN, while 3% were FP, 9% were FN, and 2% were TP (**Table 1**). Participants in the FP group were more likely to be female, black, and tended to have lower triglycerides (**Table 1**). Among the TP group, participants were less likely to be female and have hypertension, more likely to have a parental history of diabetes, and tended to have higher triglycerides and ACR (**Table 1**). Those with hyperglycemia (2-hour ≥200 mg/dL and/or fasting glucose ≥126 mg/dL) irrespective of 1,5-AG (FN, TP) were more likely to be obese, have hypertension, have parental history of diabetes, and tended to have higher body mass index and triglycerides and lower HDL compared to those without hyperglycemia (2-hour <200 mg/dL and fasting glucose <126 mg/dL [TN, FP]; **Table 1**).

In total, there were 1,750 cases of incident diagnosed diabetes (median follow-up of 15.8 years), 1,334 chronic kidney disease events (median follow-up of 15.7 years), 808 cardiovascular disease events (median follow-up of 17.7 years), and 1,788 deaths (median follow-up of 17.8 years). Categorical analyses suggested that compared to 1,5-AG ≥10 µg/mL, 1,5-AG <10 µg/mL was associated with increased risk of incident diabetes, and may be associated with future chronic kidney disease, cardiovascular

disease, and all-cause mortality (**Table 2**). 2-hour glucose ≥200 mg/dL and fasting glucose ≥126 mg/dL were statistically significantly associated with increased risk of all outcomes compared to their reference categories (**Table 2**). Adjustment for additional covariates did not alter our inferences (**Table E-1**).

When modeled with restricted cubic splines, values of 1,5-AG below the tenth percentile (12.3 μg/mL) were associated with incident diagnosed diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality in the primary unadjusted analysis (**Figure 1, Panel A**). The lowest levels of 1,5-AG were associated with the highest risk of future outcomes, although risk was not linear across the entire distribution. Higher values of 2-hour glucose (200 mg/dL) and fasting glucose (116 mg/dL) were strongly associated with incident diagnosed diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality (**Figure 1, Panels B and C**). When comparing the models using Harrell's c-statistic, 2-hour glucose and fasting glucose provided more prognostic value for future adverse events than 1,5-AG (**Table 3**). These comparisons remained irrespective of adjustment for most covariates (**Table E-2**).

Our analysis of the cross-tabulations of 1,5-AG with fasting and 2-hour glucose revealed that in the absence of hyperglycemia (low fasting [<126 mg/dL] and 2-hour [<200 mg/dL] glucose), 1,5-AG <10 μg/mL (FP) was significantly associated with future diagnosed diabetes (HR: 1.37, 95% CI: 1.06, 1.78; **Table 4**). Hyperglycemia categories (2-hour ≥200 mg/dL and/or fasting glucose ≥126 mg/dL [FN, TP]) irrespective of 1,5-AG were associated with incident diagnosed diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality (**Table 4**). Results were similar after adjustment (**Table E-3**). Despite the fact that the TP group was at the highest risk, 1,5-AG did not provide

additional information for risk stratification when we assessed increases in Harrell's c-statistic when added to unadjusted continuous models of 2-hour glucose and/or fasting glucose (differences in c-statistic of model with 2-hour glucose, fasting glucose, and 2-hour glucose and fasting glucose-those models + 1,5-AG were not statistically significantly different than 0 for all outcomes; *data not shown*).

Discussion

In our comparison of 1,5-AG and 2-hour glucose for risk of future adverse outcomes among persons without diagnosed diabetes, we observed that low values of 1,5-AG were indicative of increased risk of incident diagnosed diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality. Consistent with prior studies[9,10] and the biology of 1,5-AG, the signal for adverse outcomes seemed to be largely driven by those persons with 1,5-AG concentrations <10 μg/mL, meaning risk associations for 1,5-AG demonstrated a clear threshold effect, with virtually no risk associations observed at higher 1,5-AG values. Nonetheless, the prognostic value of 1,5-AG was less than that of 2-hour or fasting glucose for the same outcomes.

We also tested whether 1,5-AG could add prognostic information above and beyond fasting or 2-hour glucose, but did not find evidence of its incremental contribution. In general, our results suggest the utility of 1,5-AG outside the setting of diabetes—for instance, as a screening test alone or in combination with glucose to identify individuals at high risk of future outcomes—is likely to be limited.

We did find that persons with "isolated low 1,5-AG" (persons with 2-hour glucose <200 mg/dL and fasting glucose <126 mg/dL, but 1,5-AG <10 μg/mL; FP) were at high risk for future diabetes. This finding is provocative. Causes of low 1,5-AG outside

the setting of hyperglycemia are largely uncharacterized but potential non-glycemic determinants include diet,[22–24] kidney function,[25] liver disease,[26] and genetic variants related to glucose metabolism[27]. Another explanation is that these individuals were misclassified by both 2-hour glucose and fasting glucose but identified as having disordered glucose metabolism by 1,5-AG. Controlled studies are needed to better understand determinants of low 1,5-AG outside of hyperglycemia.

Our study was among the first to directly compare associations of 1,5-AG and 2-hour glucose in a large, community-based U.S. population with rigorous ascertainment of major clinical outcomes. Additional strengths included the detailed phenotypic characterization of the population and long duration of follow-up. Some limitations of this study that should be considered in the interpretation of our results include that we only had a single measure of each biomarker. And although 1,5-AG was measured in samples from the same visit as 2-hour glucose, these assays were conducted in stored samples, many years later. Cases of incident diagnosed diabetes during the follow-up period in this study would have been identified largely on the basis of glucose (HbA1c was not recommended for diagnosis of diabetes until 2010[28]), and elevated values of glucose (2-hour ≥300 mg/dL; fasting glucose ≥200 mg/dL) were reported back to participants. Therefore, it was likely that glucose measures would be more strongly associated with incident diabetes.

In summary, we observed that associations of 1,5-AG with adverse outcomes were not as strong as 2-hour or fasting glucose among persons without diagnosed diabetes. It is unlikely that 1,5-AG is a feasible routine screening test for undiagnosed diabetes in the general population. However, we identified a group of individuals with

isolated low 1,5-AG who were at increased risk of future diabetes. The reasons for "isolated" low 1,5-AG are largely uncharacterized and it is not clear why individuals might have low values of 1,5-AG without concurrent hyperglycemia. Further understanding the determinants of low 1,5-AG outside of the setting of diabetes is important to continue to inform its utility in clinical practice.

Table 1. Baseline risk factors by hyperglycemia and 1,5-AG concordance categories among those without prevalent diabetes, chronic kidney disease, or cardiovascular disease, n=6,644

	No hyperglycemia		Hyperglycemia	
	True Negative (TN) 2-hour <200 mg/dL, fasting glucose <126 mg/dL, and 1,5-AG ≥10 µg/mL	**False Positive (FP)** 2-hour <200 mg/dL, fasting glucose <126 mg/dL, and 1,5-AG <10 µg/mL	**False Negative (FN)** 2-hour ≥200 mg/dL and/or fasting glucose ≥126 mg/dL, and 1,5-AG ≥10 µg/mL	**True Positive (TP)** 2-hour ≥200 mg/dL and/or fasting glucose ≥126 mg/dL, and 1,5-AG <10 µg/mL
	N=5681	N=220	N=610	N=133
Age (years)	62.6 (5.5)	63.4 (6.1)	64.4 (5.6)	63.3 (5.4)
Female, %	59.2	66.4	63.9	51.9
Black, %	16.0	22.7	18.2	21.1
Body mass index (kg/m^2)	28.2 (5.3)	27.5 (5.2)	30.3 (5.8)	30.8 (5.6)
Obese, %	30.2	28.2	47.4	51.1
Fasting glucose (mg/dL)	98.1 (8.8)	98.1 (9.4)	119.5 (21.1)	167.8 (61.9)
2-hour glucose (mg/dL)	123.0 (33.0)	124.7 (31.1)	226.0 (38.5)	299.7 (87.3)
1,5-AG (µg/mL)	20.9 (5.5)	7.5 (2.2)	19.0 (5.4)	6.0 (2.9)
Total cholesterol (mg/dL)	202.5 (35.5)	199.2 (36.2)	203.4 (38.9)	205.9 (37.1)
HDL cholesterol (mg/dL)	52.0 (16.6)	55.2 (18.2)	46.9 (15.4)	43.3 (14.1)
Triglycerides (mg/dL)	134.9 (75.4)	123.4 (60.6)	171.7 (95.5)	198.7 (142.4)
Hypertension, %	38.1	38.6	61.1	46.6
Less than high school, %	14.3	15.5	20.8	18.0
Current smoker, %	14.0	14.1	12.0	9.8
Current drinker, %	55.6	59.1	48.2	50.4
Parent history of diabetes, %	21.1	24.5	30.7	38.3
$eGFR_{cr}$ (ml/min/1.732 m^2)	88.2 (12.5)	87.6 (12.8)	88.0 (12.7)	91.4 (12.5)
ACR (Median, IQR; ug/mg)	3.4 (1.8, 6.4)	3.9 (1.9, 7.1)	3.7 (1.6, 7.4)	5.1 (2.0, 10.6)

Abbreviations: 1,5-AG, 1,5-anhydroglucitol; $eGFR_{cr}$, estimated glomerular filtration rate (creatinine); ACR, albumin-to-creatinine ratio

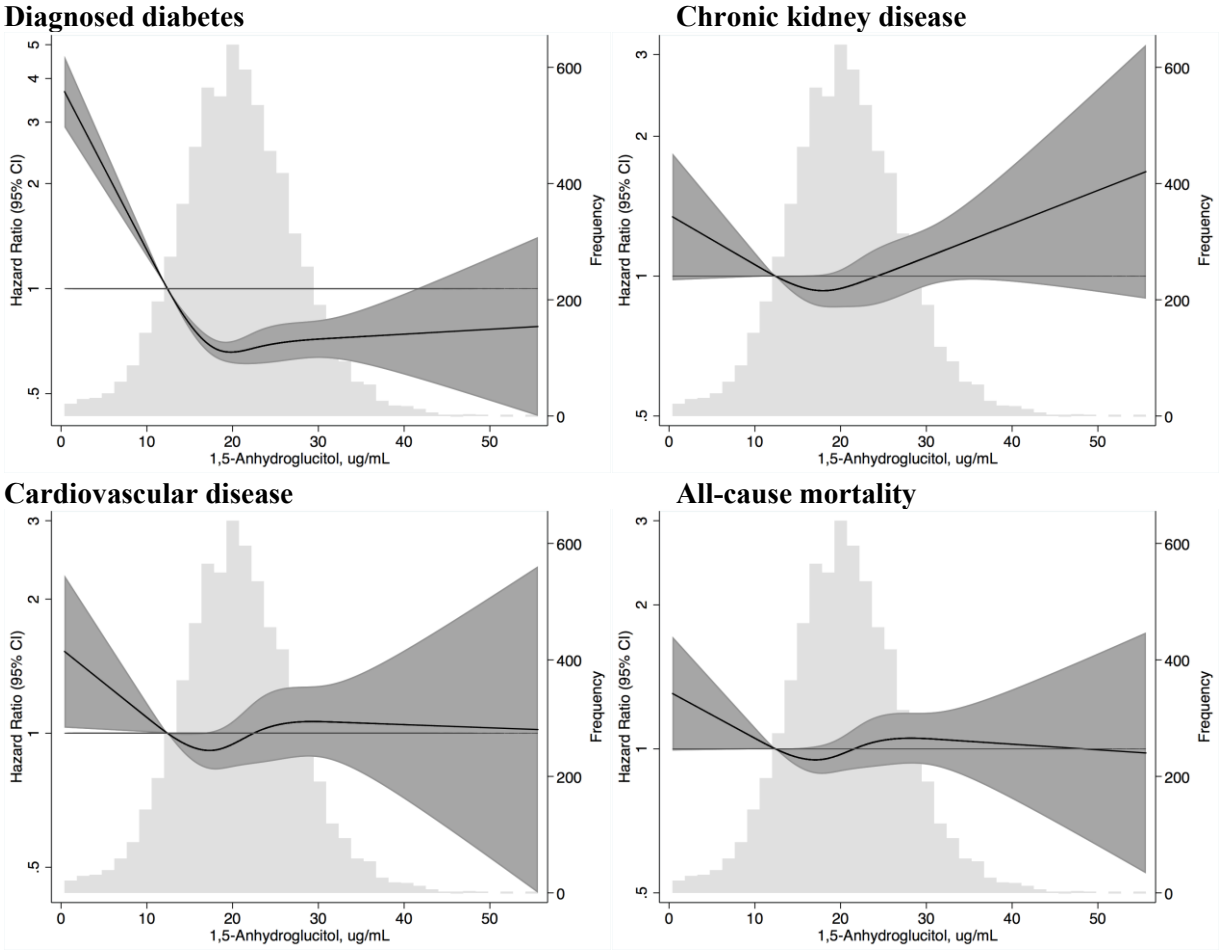
Table 2. Unadjusted hazard ratios and 95% CI of categories of 1,5-AG, 2-hour glucose, and fasting glucose for risk of incident diagnosed diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality, n=6,644

Biomarker Categories		Diagnosed diabetes		Chronic kidney disease	
	n	Events	HR (95% CI)	Events	HR (95% CI)
1,5-AG ≥10 µg/mL	6,291	1,575	1 (REF)	1,253	1 (REF)
1,5-AG <10 µg/mL	353	175	**2.70** (2.31, 3.15)	81	1.19 (0.95, 1.49)
2-hour glucose <200 mg/dL	5,970	1,275	1 (REF)	1,163	1 (REF)
2-hour glucose ≥200 mg/dL	674	475	**6.68** (6.00, 7.43)	171	**1.46** (1.25, 1.72)
Fasting glucose <126 mg/dL	6,315	1,458	1 (REF)	1,250	1 (REF)
Fasting glucose ≥126 mg/dL	329	292	**13.8** (12.1, 15.7)	84	**1.48** (1.19, 1.85)
		Cardiovascular disease		**All-cause mortality**	
	n	Events	HR (95% CI)	Events	HR (95% CI)
1,5-AG ≥10 µg/mL	6,291	756	1 (REF)	1,685	1 (REF)
1,5-AG <10 µg/mL	353	52	1.27 (0.96, 1.68)	103	1.12 (0.92, 1.37)
2-hour glucose <200 mg/dL	5,970	690	1 (REF)	1,544	1 (REF)
2-hour glucose ≥200 mg/dL	674	118	**1.64** (1.35, 1.99)	244	**1.51** (1.32, 1.73)
Fasting glucose <126 mg/dL	6,315	745	1 (REF)	1,660	1 (REF)
Fasting glucose ≥126 mg/dL	329	63	**1.79** (1.39, 2.32)	128	**1.63** (1.36, 1.95)

Bold indicates $p<0.05$

Figure 1. Distributions and unadjusted associations of 1,5-AG, 2-hour glucose, and fasting glucose with incident diagnosed diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality modeled with restricted cubic splines, n=6,644

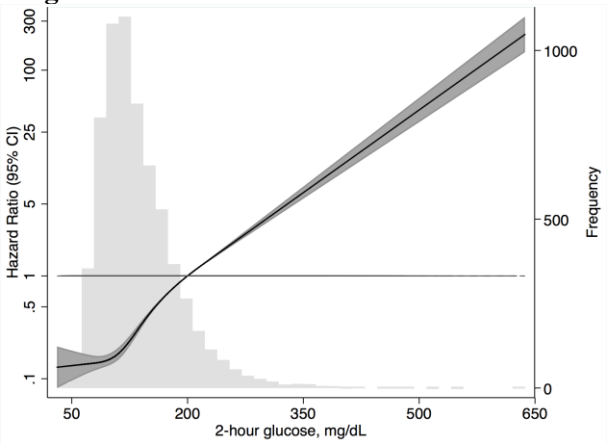
PANEL A. 1,5-AG



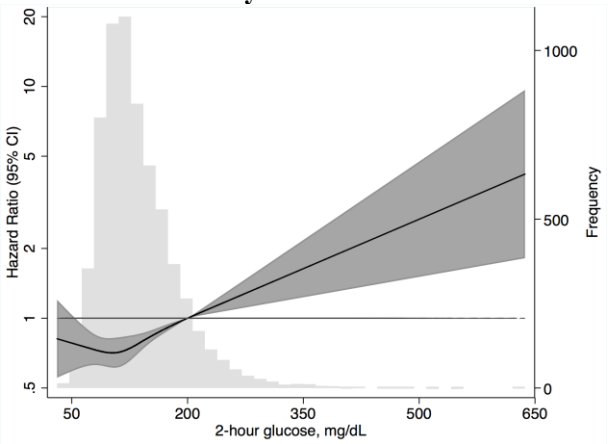
Models centered at 10th percentile: 12.3 µg/mL; note different scale of y-axis (HR 95%CI) for incident diagnosed diabetes
Abbreviations: 1,5-AG, 1,5-anhydroglucitol; CI, confidence interval

PANEL B. 2-hour glucose

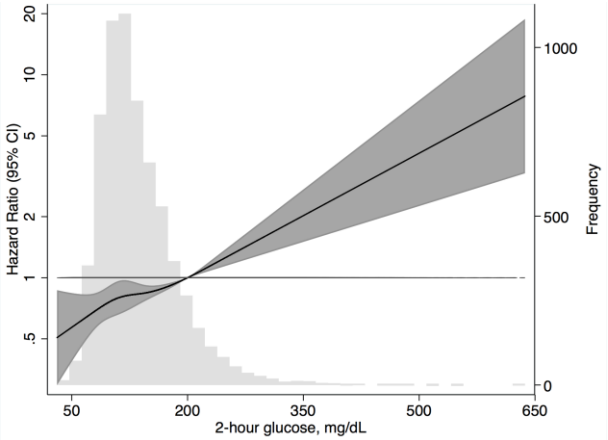
Diagnosed diabetes



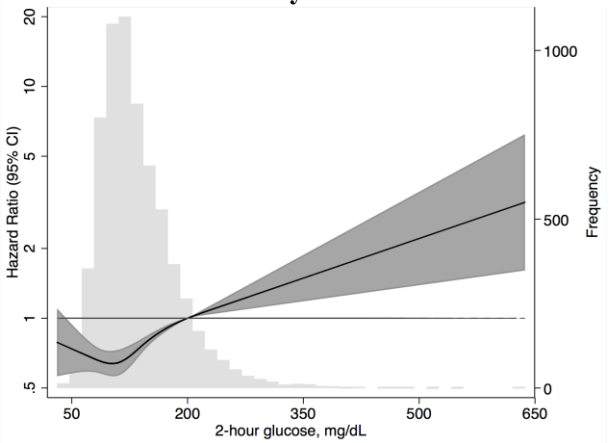
Chronic kidney disease



Cardiovascular disease



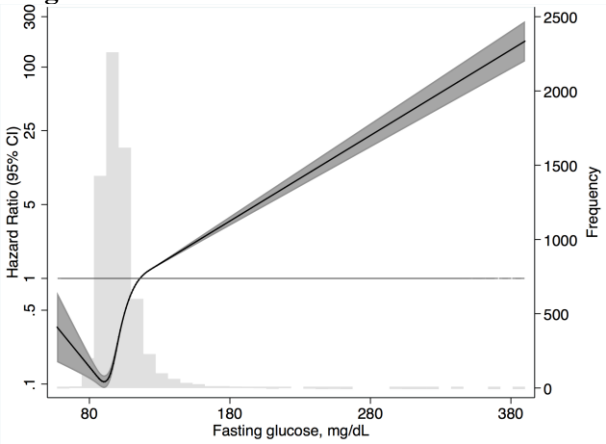
All-cause mortality



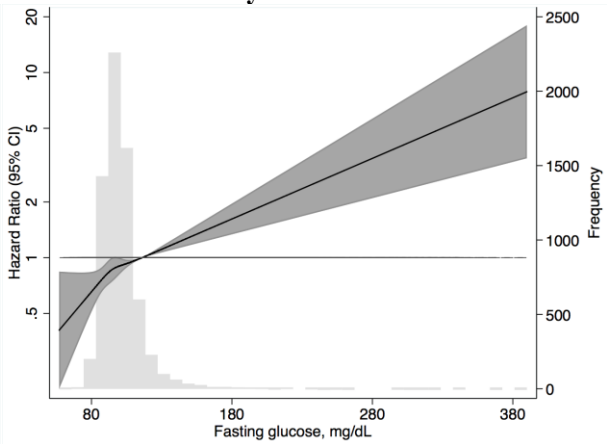
Models centered at 90th percentile: 200 mg/dL; note different scale of y-axis (HR 95%CI) for incident diagnosed diabetes
Abbreviations: 1,5-AG, 1,5-anhydroglucitol; CI, confidence interval

PANEL C. Fasting glucose

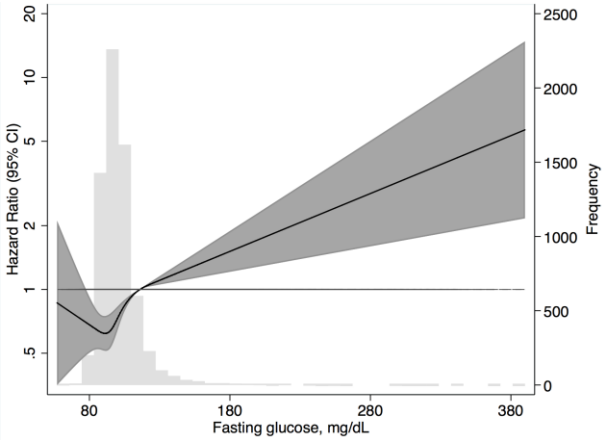
Diagnosed diabetes



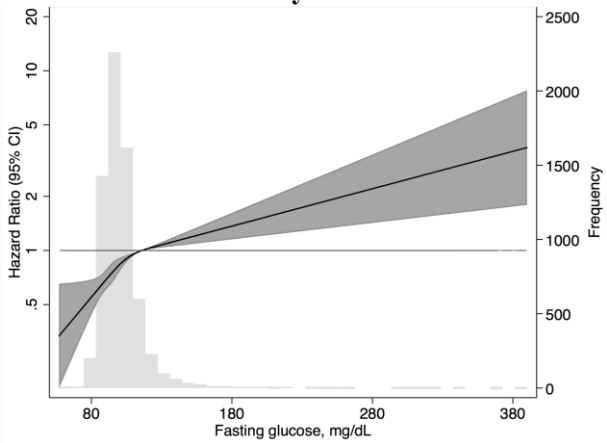
Chronic kidney disease



Cardiovascular disease



All-cause mortality



Models centered at 90th percentile: 116 mg/dL; note different scale of y-axis (HR 95%CI) for incident diagnosed diabetes
Abbreviations: 1,5-AG, 1,5-anhydroglucitol; CI, confidence interval

Table 3. Differences in Harrell's C-statistics from unadjusted associations of 1,5-AG, 2-hour glucose, and fasting glucose with incident diagnosed diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality modeled with restricted cubic splines, n=6,644

	Differences in Harrell's C-statistic (95% CI)			
	Diagnosed diabetes	**Chronic kidney disease**	**Cardiovascular disease**	**All-cause mortality**
2-hour glucose – 1,5-AG	**0.17** (0.15, 0.19)	**0.02** (0.00, 0.05)	**0.03** (0.00, 0.06)	**0.04** (0.02, 0.06)
Fasting glucose – 1,5-AG	**0.18** (0.17, 0.20)	0.02 (0.00, 0.04)	**0.05** (0.02, 0.07)	**0.04** (0.02, 0.06)

Bold indicates $p<0.05$

Abbreviations: 1,5-AG, 1,5-anhydroglucitol; CI, confidence interval

Table 4. Unadjusted hazard ratios and 95% CI of categories of hyperglycemia and 1,5-AG concordance for risk of incident diagnosed diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality, n=6,644

Categories of Hyperglycemia and 1,5-AG concordance	Diagnosed diabetes			Chronic kidney disease	
	n	Events	HR (95% CI)	Events	HR (95% CI)
True Negative (TN)	5681	1166	1 (REF)	1112	1 (REF)
False Positive (FP)	220	59	**1.37** (1.06, 1.78)	39	0.89 (0.65, 1.22)
False Negative (FN)	610	409	**6.10** (5.45, 6.84)	141	**1.29** (1.09, 1.54)
True Positive (TP)	133	116	**15.9** (13.1, 19.3)	42	**1.89** (1.39, 2.58)
	Cardiovascular disease			**All-cause mortality**	
	n	Events	HR (95% CI)	Events	HR (95% CI)
True Negative (TN)	5681	653	1 (REF)	1466	1 (REF)
False Positive (FP)	220	27	1.09 (0.74, 1.60)	55	0.98 (0.75, 1.28)
False Negative (FN)	610	103	**1.59** (1.29, 1.96)	219	**1.49** (1.29, 1.72)
True Positive (TP)	133	25	**1.77** (1.19, 2.64)	48	**1.52** (1.14, 2.02)

Bold indicates $p<0.05$

Abbreviations: 1,5-AG, 1,5-anhydroglucitol; CI, confidence interval

Conclusion

This dissertation investigated epidemiological questions related to screening for prediabetes and diabetes. Identifying asymptomatic individuals at risk for diabetes and its related adverse outcomes is critical to reduce the disease burden and identify opportunities for prevention. To address key gaps in the literature, we characterized trajectories of kidney function by diabetes status over time, evaluated the comparative prognostic performance of five different definitions of prediabetes—all of which are in current clinical use—and interrogated whether a novel biomarker, 1,5-anhydroglucitol, might have a role for diabetes screening and risk stratification.

Summary of Findings and Implications

Chapter 1 analyses characterized trajectories of kidney function by diabetes status with up to four measurements of serum creatinine per person and over 25 years of follow-up. We observed that persons with diabetes have a decline in kidney function that was much more steep (approximately twice the rate of decline) than those without diabetes. We also observed that persons with undiagnosed diabetes decline more steeply than those without diabetes, after an initial period of less steep average decline, which may suggest a period of hyperfiltration. Additionally, we identified subgroups of persons with diabetes with genetic, demographic, and modifiable risk factors that may indicate risk of steeper decline.

These results provide information on expected decline by diabetes status, emphasize the risk of kidney function decline in persons with diabetes, and should inform the design and conduct of clinical trials that use eGFR as a surrogate endpoint. This

research also highlights the importance of diabetes screening to identify persons at risk for kidney disease, the need for rigorous monitoring of kidney parameters and glycemic control in persons with diagnosed diabetes to prevent kidney function decline.

Chapter 2[1] directly compared the five different definitions of prediabetes which have been recommended by different international diabetes organizations. All five of these definitions are in current clinical use, causing confusion regarding which group of persons truly has prediabetes and which definition might be optimal for screening in the general population. Indeed, we observed that the prevalence of prediabetes—in a single population—ranged from 9% to 38%, depending on the definition used. The American Diabetes Association (ADA) fasting glucose-based definition resulted in the largest prevalence estimate, while the International Expert Committee HbA1c-definition identified the smallest group of people. The characteristics of persons with prediabetes by the different definitions also varied, with HbA1c-based definitions identifying those with worse cardiometabolic risk profiles.

Following participants for up to 22 years for incident diabetes, chronic kidney disease, atherosclerotic cardiovascular disease, peripheral arterial disease, and all-cause mortality, we compared the test characteristics and prognostic value of the various definitions. We saw that prediabetes was a high-risk condition for future outcomes regardless of definition. Comparatively, we observed that HbA1c-based prediabetes definitions and the World Health Organization (WHO) fasting glucose-based definition were more specific for identification of future outcomes than the ADA fasting glucose-based definition. Glucose-based definitions (ADA fasting glucose, ADA and WHO 2-hour glucose), with the exception of WHO fasting glucose, had higher sensitivity.

HbA1c-based definitions had higher incidence rates and larger hazard ratios and c-statistics for chronic kidney disease, atherosclerotic cardiovascular disease, peripheral arterial disease, and all-cause mortality.

The results of this analyses supports a call for action to obtain international consensus on definitions of prediabetes. The drastically varying proportions of people identified by the different definitions demonstrate the importance of consistency for public health efforts and coordination of prevention programs. Formal recommendations to help guide the choice of prediabetes definition under different scenarios are needed to help inform resource allocation and program planning.

Chapter 3 was a diagnostic screening study, comparing 1,5-anhydroglucitol (1,5-AG) to 2-hour glucose for identification of undiagnosed diabetes. We observed substantial discordance between low 1,5-AG and categories of hyperglycemia defined by 2-hour glucose and fasting glucose. Categories of 1,5-AG resulted in low sensitivity but high specificity for identification of undiagnosed diabetes defined by 2-hour glucose regardless of the 1,5-AG cut point used. Comparing continuous values of the two markers in receiver operating characteristic (ROC) analyses resulted in similar conclusions.

Through this study, we also identified a group of individuals with "low isolated 1,5-AG", or those with low 1,5-AG but no hyperglycemia defined by the glucose measures. The characteristics associated with this provocative group were age, black race, decreased kidney function, and increased kidney damage. While we concluded that 1,5-AG is unlikely to be a useful screening test in the community, further understanding those with low isolated 1,5-AG may further inform its utility.

In *Chapter 4,* we compared the associations of 1,5-AG and 2-hour glucose for risk of incident diabetes, cardiovascular disease, chronic kidney disease, and all-cause mortality. We observed that 1,5-AG was not as strongly associated with risk of future outcomes as 2-hour glucose, and that risk was not continuous across the distribution. We also saw that those with "low isolated 1,5-AG" were at high risk of future diabetes. This suggests that there could have been misclassification by both 2-hour glucose and fasting glucose.

It also highlights that although the lowest values of 1,5-AG may be largely influenced by hyperglycemia, there are likely a number of factors that influence the remaining values in the distribution including diet[2,3], kidney function[4], liver disease[5], and genetic variants that influence glucose metabolism[6]. Controlled studies are needed to further understand this heterogeneous group missed by traditional screening tests that are at increased risk for diabetes.

The *Methodological Supplement* described a calibration study that was conducted to statistically correct our Visit 4 1,5-AG plasma measurements (conducted in 2015-2016 at the Atherosclerosis Clinical Research Laboratory at the Baylor College of Medicine) to align them with prior Visit 2 and Visit 5 serum 1,5-AG measurements (conducted in 2011-2013 at the Advanced Research and Diagnostic Laboratory at the University of Minnesota). We also derived a correction to account for substantial drift over time that was observed during 2015-2016 in the Visit 4 1,5-AG measurements. This work helps minimize potential bias in epidemiologic analyses using these data and improves the comparability of 1,5-AG measurements conducted across two laboratories.

Future Directions

Answering open questions regarding hyperfiltration

Our results suggest that hyperfiltration may occur early in the course of diabetes. Given that persons with new onset diabetes may be particularly targeted for prevention of chronic kidney disease progression, further understanding this complex relationship would have great clinical utility. Better understanding of whether hyperfiltration occurs, the period of time for which it occurs, characteristics of the persons in which it occurs, and whether it is indicative of higher risk of adverse outcomes is important.

Data on serial measurements of creatinine over 4 years among Pima Indians without diabetes, impaired glucose tolerance, newly diagnosed diabetes, and established diabetes[7], which in part, prompted this line of investigation, should be replicated and extended in a community-based population, if possible. However, the natural history of diabetes and kidney function will be more difficult to assess using modern data given that some newer diabetes medications have significant interplay with the kidney. If existing datasets have more measurements of serum creatinine in shorter-time frames with information on diabetes duration, this question should be pursued.

Better definitions of prediabetes?

Reaching consensus on a definition of prediabetes is critical for public health coordination and planning, but it is also important to recognize that all of our current definitions have limitations. Some experts have criticized the entire category of "prediabetes" especially as incidence rates of progression from prediabetes to diabetes are low[8]. Although data are sparse and conversion also depends on the definition in use, studies estimate that half to two-thirds of persons with prediabetes will not have diabetes in 10 years[8,9]. That some persons with prediabetes never go on to develop diabetes also

complicates resource allocation and planning. Experts have advocated for a multidimensional approach and the development of risk-based definitions of prediabetes that incorporate glycemic variables plus additional factors[10,11]. Developing a new method to identify those with prediabetes who are at high-risk for developing diabetes would be useful in both clinical practice and public health planning.

Future utility of 1,5-AG

1,5-AG is approved by the U.S. Food and Drug Administration for short-term monitoring of glycemic control among persons with diabetes, is currently being marketed for use in the U.S. by GlycoMark®, and is reimbursed by Medicare, Medicaid, and most private insurers. However, the evidence for its clinical utility is still developing and there are a number of open questions. Epidemiological studies, similar to the ones we conducted, provide useful information on how tests like 1,5-AG perform in the general population.

We saw in the setting outside of diagnosed diabetes that its potential to substitute for existing more burdensome markers, like 2-hour glucose, is limited. However, there is evidence that 1,5-AG may provide information above and beyond traditional markers of glycemia to identify those at high risk for adverse outcomes at least among persons with diabetes[12,13]. Whether that additional information leads to better clinical outcomes is less clear. Exploring whether panels of non-fasting biomarkers measured at one time, which would limit participant burden and provide more information, could be helpful. Further, understanding whether the additional information gained is associated with improved clinical outcomes is critical.

1,5-AG could also have other uses. For example, 1,5-AG could provide means to better risk stratify particular subgroups, for example, older adults with diabetes. Diabetes in older adults is a very heterogeneous condition with open questions about who should receive treatment. Given its specificity, 1,5-AG could provide information to better identify high-risk individuals.

We should continue to search for alternative biomarkers given limitations of current measures and to develop more epidemiologic data that assess performance in general populations. Future studies are needed to build the evidence base and continue to understand the clinical utility of measures like 1,5-AG.

Summary

This dissertation extended the existing epidemiological evidence base of screening for prediabetes and diabetes. Future research in this line of investigation is needed to refine who is at highest risk of prediabetes, diabetes, and their associated complications and who may most benefit from preventative measures. Informing allocation of clinical and public health resources will remain critical as this pressing public health problem continues to grow.

Appendices

Appendix A: Methodological supplement

Summary

Existing measurements of 1,5-anhydroglucitol (1,5-AG) are available at visit 2 and visit from serum samples measured at the University of Minnesota in 2011-2013. Subsequent measurements of 1,5-AG were conducted in stored visit 4 plasma samples at Baylor College of Medicine from 2015-2016. To ensure comparability to previous measurements conducted at the University of Minnesota (visit 2 and visit 5 serum samples in 2011-2013), we performed a calibration study using visit 5 samples from University of Minnesota and Baylor College of Medicine. We applied the serum-plasma Deming regression equation and conducted additional correction by time for 1,5-anhydroglucitol.

Amended visit 4 1,5-anhydroglucitol values were stored in a cleaned data set for use:

(File Name: /Volumes/ARIC$/Special Projects/V4 Glycemic Markers/STATA data/v4_glycemicmarkers_v2.dta).

Background

1,5-AG (GlycoMark) was measured in plasma on the Beckman/Olympus AU480 autoanalyzer at Baylor College of Medicine (Baylor, Ballantyne/Hoogeveen) as part of Ancillary #2009.16 (PI: Selvin). These tests were coordinated with Ancillary Studies #2013.20 and #2013.21 (PI: Ballantyne) and were conducted in the same visit 4 plasma samples and run on the same autoanalyzers, using incremental volume only. This visit 4 testing took place from July 2015-August 2016.

1,5-AG was previously measured at visits 2 and 5 with the same assays, but in serum samples and using the Roche Modular P800 instrument at the University of Minnesota (UMN, Steffes/Eckfeldt).

To ensure the comparability of the Baylor measurements to those previously assessed at UMN, we conducted a 2-step calibration study:

(a) Serum-to-serum preliminary comparison: 50 randomly selected visit 5 IDs (25 with and 25 without diagnosed diabetes) to conduct serum-to-serum comparison using visit 5 serum samples stored at Baylor. This study compared lab-to-lab differences of visit 5 serum measurements. This study compared previously measured serum measurements conducted at the University of Minnesota (Roche Modular P800) to the same biomarkers measured in stored visit 5 serum samples at Baylor College of Medicine using the Beckman Olympus 480 auto analyzer (UMN serum measurements as reference). This serum-to-serum preliminary comparison study informed the serum-to-plasma calibration study.

(b) Serum-to-plasma laboratory calibration study: 200 randomly selected visit 5 IDs to conduct a formal calibration study in visit 5 plasma samples stored at Baylor to ensure comparability to previous visit 5 serum measurements conducted at UMN (serum UMN measurements as reference). This serum-to-plasma calibration study enabled generation of re-calibration equations between the measurements at Baylor in plasma compared to UMN in serum. We then applied those equations to the visit 4 measurements when there was a difference > 10%.

Table A-1. Overview of study sample and corresponding visit, sample type, lab, and auto-analyzer

Measurements	N	Sample type	Lab	Auto-analyzer
Visit 5 Preliminary Comparison Study Samples *(Reference)*	50	Serum	University of Minnesota	Roche Modular P800
Visit 5 Preliminary Comparison Study Samples	50	Serum	Baylor College of Medicine	Olympus 480
Visit 5 Calibration Study Samples	200	Plasma	Baylor College of Medicine	Olympus 480
Visit 5 Calibration Study Samples *(Reference)*	200	Serum	University of Minnesota	Roche Cobas 6000
Visit 4 Measurements in All Participants *To which calibration equations will be applied, as needed*	~10,400	Plasma	Baylor College of Medicine	Olympus 480

Methods

To enable comparison of new visit 4 measurements with previous measurements, we formally compared measurements conducted in different laboratories and in different sample types/methodologies and documented systematic differences and corrected any observed "laboratory drift". We implemented a standard process used previously [110], as described below:

(1) Iteratively identified outliers +/- 3SD from difference of measurements for both the preliminary comparison and calibration studies

(2) Assessed agreement between the two measurements by Pearson's correlations, scatterplots, Bland-Altman plots again for both the preliminary comparison and calibration studies

(3) Conducted Deming regression using serum (UMN) measurements as the dependent variable and plasma (Baylor) measurements as the independent variable to generate recalibration equations (calibration study)

(4) Corrected measurements with differences > 10% to align visit 4 measurements to UMN (calibration study)

Serum-to-Serum Preliminary Comparison Study

Corresponding .Do File(s)
/Volumes/ARIC$/Special Projects/V4 Glycemic Markers/Serum-Serum/Code/Serum-Serum Programs_v4.do /Volumes/ARIC$/Special Projects/ V4 Glycemic Markers/Serum-Serum/Code/Serum-Serum_v4.do

Table A-2. Outliers identified as +/- 3*SD of the difference and the number of iterations required for their identification

Glycemia Marker	Iteration	Number of Outliers Identified
1,5-AG (ug/mL)	0	0

Table A-3. Summary statistics and mean differences comparing Baylor (serum) to UMN (serum) measurements, excluding outliers. Outliers defined as +/- 3*SD of the difference (2 iterations maximum).

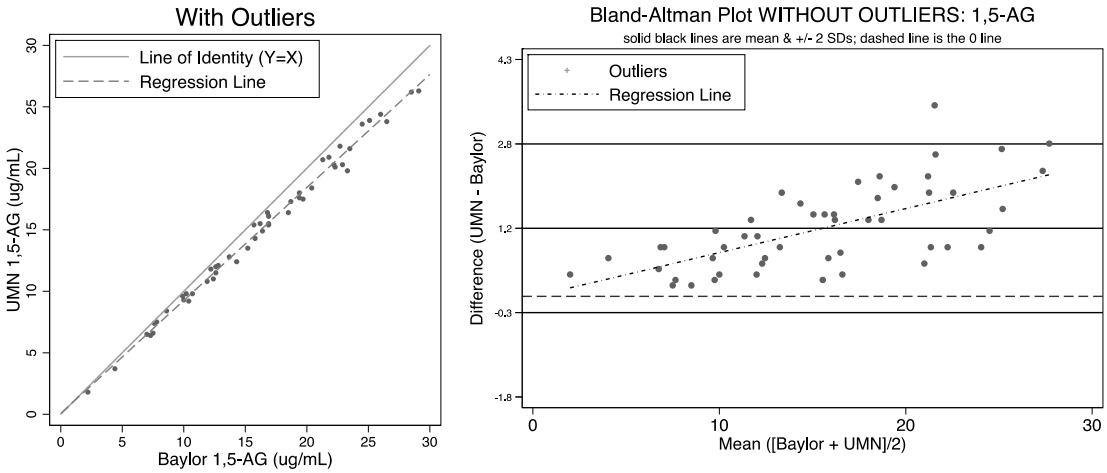
	Lab	N	Mean	SD	Median	Min	Max	*p*-value*
1,5-AG (ug/mL)	UMN	50	14.93	6.05	15.4	1.8	26.3	-
	Baylor	50	16.17	6.56	16.3	2.2	29.1	-
Difference	*UMN-Baylor*	50	**-1.25**	0.77	-1.1	-3.5	-0.20	<.001

* Test for difference between means

Table A-4. Pearson's correlation coefficients (Baylor (serum) to UMN (serum)) without inclusion of outliers. Outliers defined as +/- 3*SD of the difference (2 iterations maximum).

Glycemic Marker	Number of outliers	Correlation coefficient, outliers excluded
1,5-AG (ug/mL)	0	0.99

Figure A-1. Scatterplot and Bland-Altman Plot. Scatterplots of 1,5-AG without outliers, UMN (serum) vs. Baylor (serum). Outliers defined as +/- 3*SD of the mean difference (2 iterations). Bland-Altman plot of 1,5-AG without outliers, UMN (serum) vs. Baylor (serum). Outliers (defined as +/- 3*SD of the mean difference, 2 iterations). Y-axis tick marks are determined by SDs.



Lab-to-lab differences (all > 5%) existed when comparing measurements conducted in the same sample type (serum) at Baylor compared to UMN.

Serum-to-Plasma Calibration Study

Corresponding .Do File(s)
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Table A-5. Outliers identified as +/- 3*SD of the difference and the number of iterations required for their identification. ***Analyses that include outliers provided in the Supplement.***

Glycemia Marker	Iteration	Number of Outliers Identified
1,5-AG (ug/mL)	1	1

Table A-6. Summary statistics and mean differences comparing plasma (Baylor) to serum (UMN) measurements, excluding outliers. Outliers defined as +/- 3*SD of the difference (2 iterations maximum).

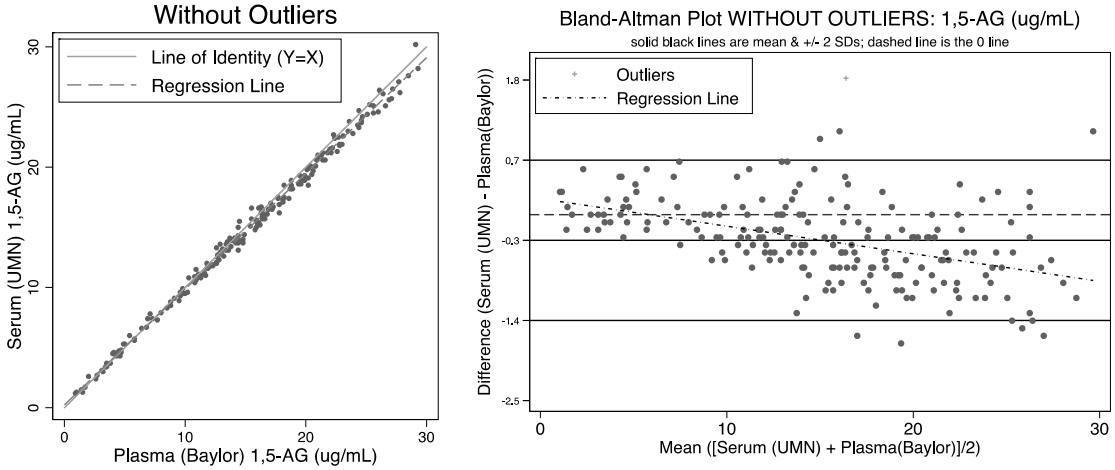
	Lab	N	Mean	SD	Median	Min	Max	*p*-value*
1,5-AG (ug/mL)	Serum (UMN)	199	15.0	6.73	15.3	1.2	30.2	-
	Plasma (Baylor)	198	15.3	6.93	15.7	0.90	29.3	-
Difference	*Serum-Plasma*	198	**-0.34**	0.53	-0.30	-1.7	1.1	<0.001

* Test for difference between means

Table A-7. Pearson's correlation coefficients (plasma [Baylor] to serum [UMN]) without inclusion of outliers. Outliers defined as +/- 3*SD of the difference (2 iterations maximum).

Glycemic Marker	Number of outliers	Correlation coefficient, outliers excluded
1,5-AG (ug/mL)	1	0.998

Figure A-2. Scatterplot and Bland-Altman Plot. Scatterplot of 1,5-AG without outliers, Serum (UMN) vs. Plasma (Baylor). Outliers defined as +/- 3*SD of the mean difference (2 iterations). Bland-Altman plot of 1,5-AG without outliers, serum (UMN) vs. plasma (Baylor). Outliers (defined as +/- 3*SD of the mean difference, 2 iterations). Y-axis tick marks are determined by SDs.



Deming Regression and Serum-Plasma Calibration

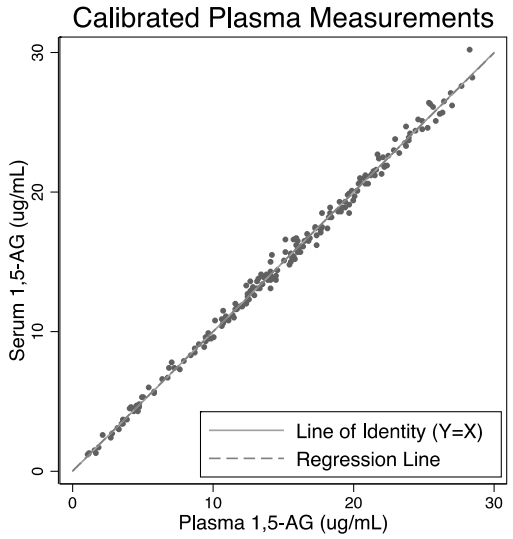
Table A-8. Deming regression results (intercept and slope) calculated with serum (UMN) measurements as dependent variable and plasma (Baylor) measurements as independent variable after exclusion of outliers

	# outliers excluded	N	*Deming Regression* Intercept	SE	*p*-value	Slope	SE	p-value	Re-calibration Formula
1,5-AG *ug/mL*	1	198	0.209	0.071	0.004	0.964	0.005	<0.001	0.964*(1,5-AG)+0.209

Table A-9. Summary statistics comparing calibrated plasma (Baylor) measurements to serum (UMN) measurements, excluding outliers. Outliers defined as +/- 3*SD of the difference (2 iterations maximum).

	Lab	N	Mean	SD	Median	Min	Max	*p*-value*
1,5-AG (ug/mL)	Serum (UMN)	199	15.0	6.73	15.3	1.2	30.2	-
	Plasma (Baylor), Calibrated	198	14.9	6.68	15.3	1.08	28.5	-
Difference	*Serum-Plasma*	198	**0.003**	0.46	-0.08	-1.18	1.94	0.935

Figure A-3. Scatterplot of calibrated 1,5-AG without outliers, serum (UMN) vs. plasma (Baylor).



Calibration of 1,5-AG

Corresponding .Do File(s)
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Prior to applying any statistical correction, we plotted the measurements over time to assess whether there were differences (**Figure A-4**). We then applied the serum-plasma correction factor from **Table A-8**, and then calibrated the values correct for differences by time using lowess (locally weighted) regression. This helped to minimize differences between visit 2, 4, and 5 measurements (**Figure A-5 a and b**).

The calibrated 1,5-AG values are provided in a dataset on the ARIC drive: /Volumes/ARIC$/Special Projects/V4 Glycemic Markers/STATA data/v4_glycemicmarkers_v2.dta)

Figure A-4. Scatterplot of Visit 4 1,5-anhydroglucitol values over time

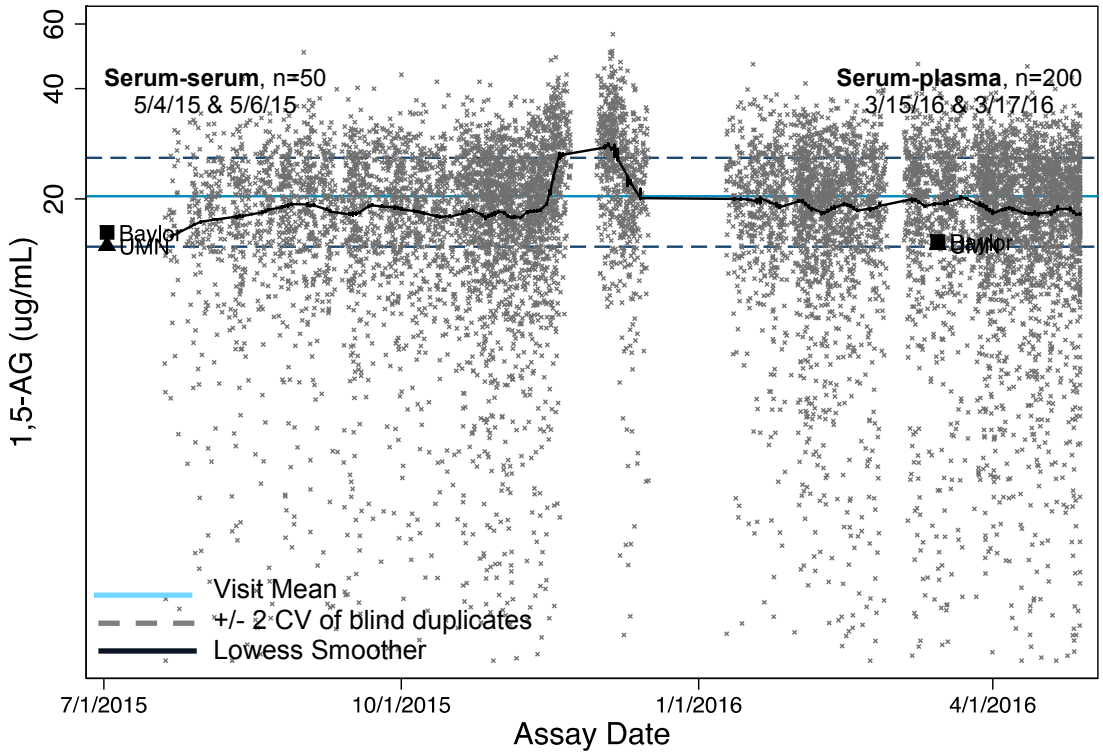
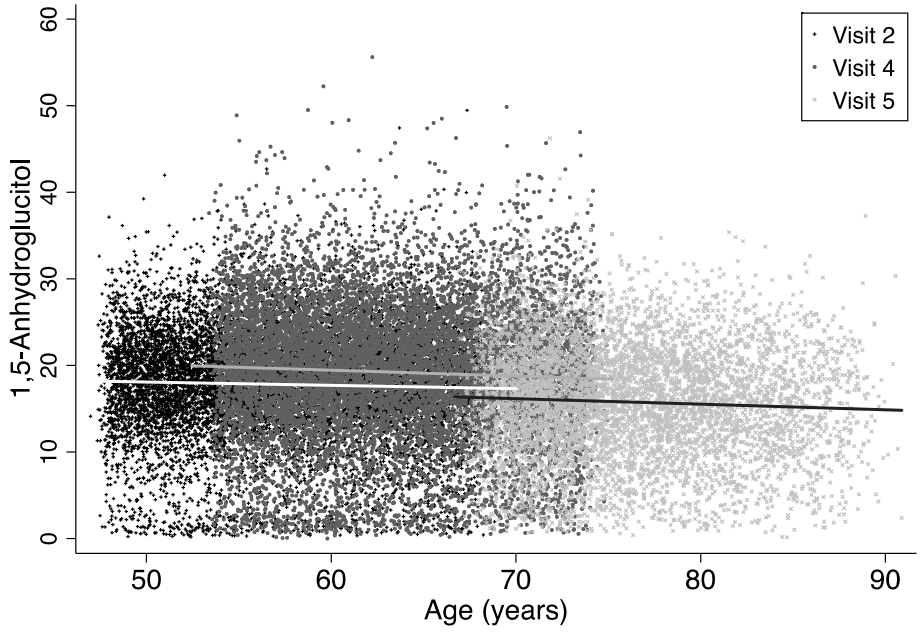


Figure A-5 (a-b). Scatterplot of Visits 2, 4, and 5 1,5-anhydroglucitol values by age

(a) Before correction



(b) After serum-plasma and lowess correction

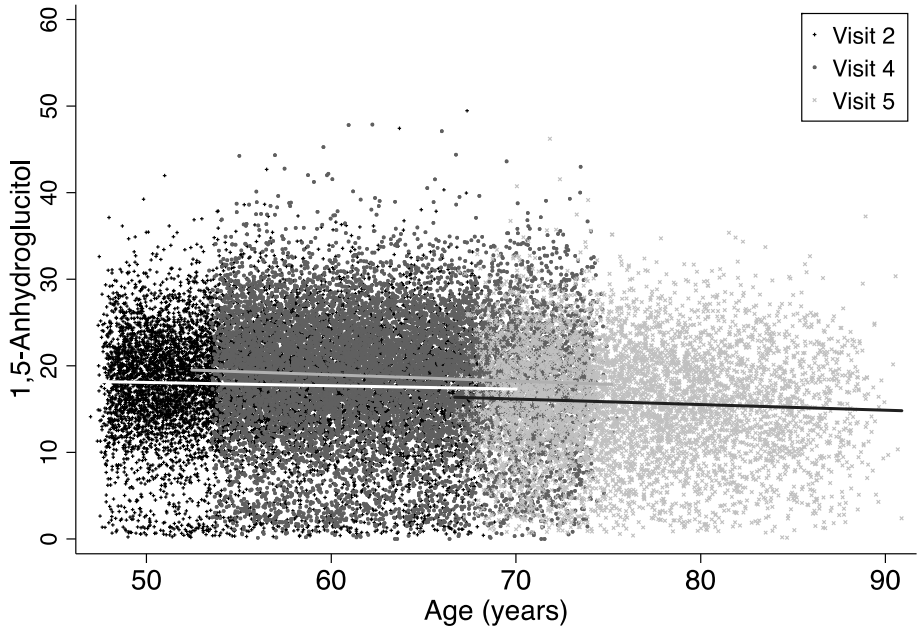


Table A-10. Summary of 1,5-AG before and after calibration.

	Lab	N	Mean	SD	Median	Min	Max	*p*-value*
1,5-AG (ug/mL)	Before correction	10383	19.2	7.82	19.6	0.1	55.6	-
	After serum-plasma and lowess correction	10383†	18.7	7.26	19.2	0.1	47.9	-
Difference	*Before-After*	10383	**0.505**	2.01	-0.06	-3.67	10.2	<0.001

* Test for difference between means

† 18 observations were imputed as 0.1, as calibration resulted in values <0

Table A-11. Correlations of 1,5-AG before and after calibration with visit 4 traditional glycemic markers, among those fasting 10 or more hours.

1,5-AG		**Overall**		**Diabetes**		**No diabetes**	
		Fasting glucose	2-hour glucose	Fasting glucose	2-hour glucose	Fasting glucose	2-hour glucose
Before correction	Pearson's *r*	-0.423	-0.248	-0.545	-0.576	-0.205	-0.220
	n	9888	8126	1024	209	8864	7917
After serum-plasma and lowess correction	Pearson's *r*	-0.437	-0.258	-0.554	-0.589	-0.216	-0.230
	n	9888	8126	1024	209	8864	7917

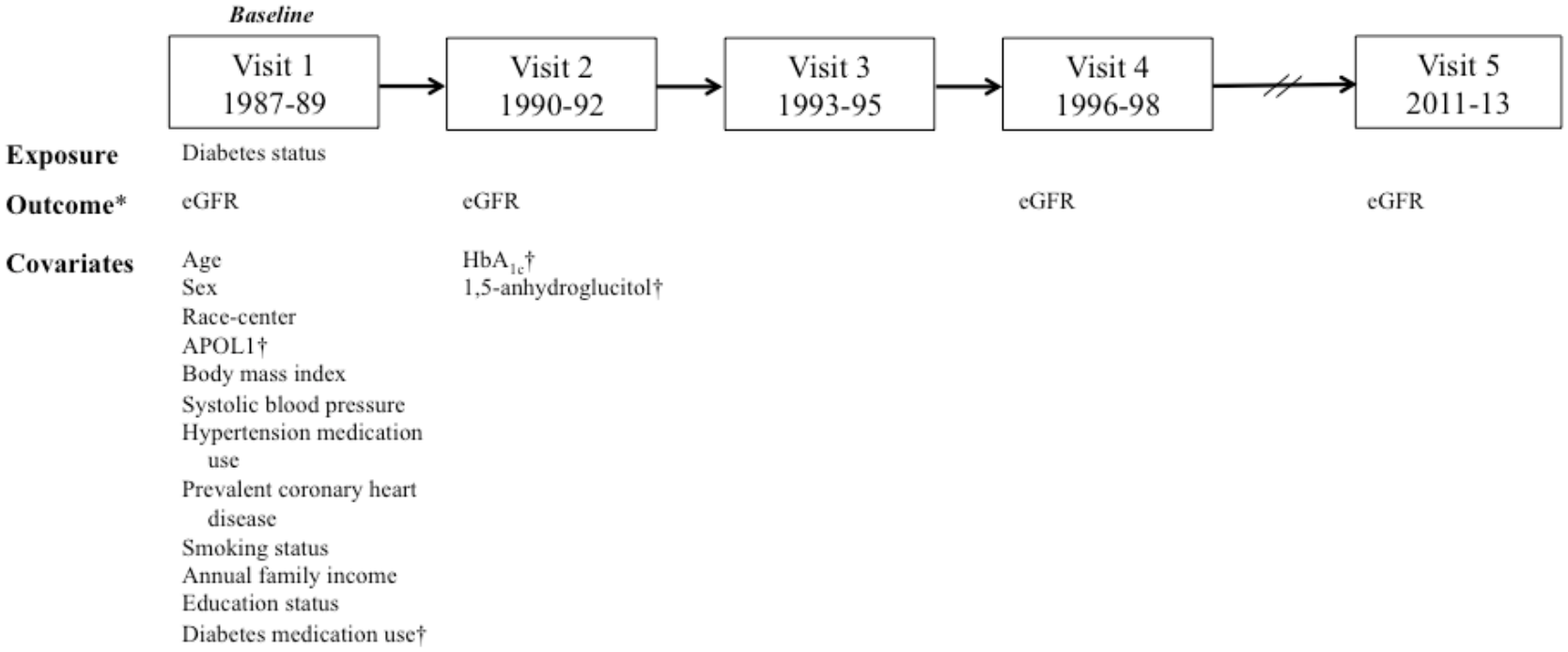
Note: trajectory analyses of 1,5-AG should still be approached with caution given values measured at visit 4 are higher, on average, than values measured at visit 2.

References

Parrinello, C. M., Grams, M. E., Couper, D., Ballantyne, C. M., Hoogeveen, R. C., Eckfeldt, J. H., … Coresh, J. (2015). Recalibration of blood analytes over 25 years in the Atherosclerosis Risk in Communities Study: Impact of recalibration on chronic kidney disease prevalence and incidence. *Clinical Chemistry*, *61*(7), 938–947. doi:10.1373/clinchem.2015.238873

Appendix B: Supplementary Materials for Chapter 1

Figure B-1. Study design and timing of measurements



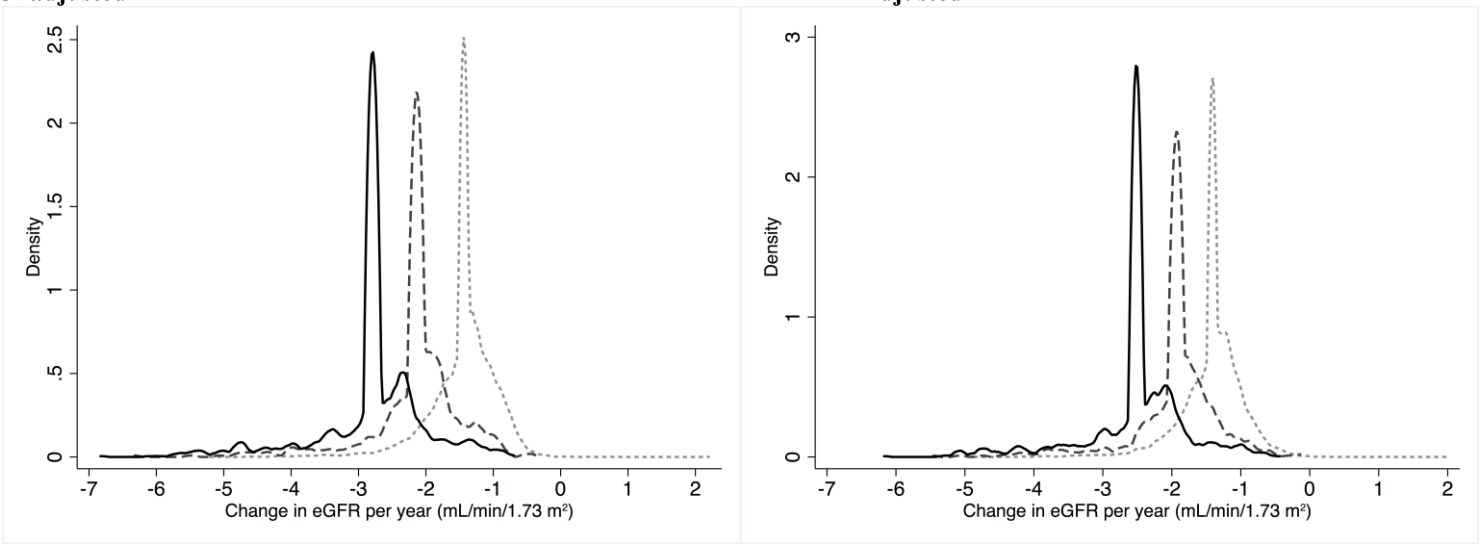
Variables used for overall analyses unless otherwise indicated

* In addition to continuous follow-up for end stage renal disease through USRDS

† Table 2

Abbreviations: *eGFR* estimated glomerular filtration rate; *HbA1c* hemoglobin A1c; *USRDS* United States Renal Data System

Figure B-2. Distribution of unadjusted and adjusted annual eGFR slopes from Visit 2 to Visit 5, by diabetes status



	Percentile and corresponding change in eGFR per year (mL/min/1.73m^2)									
	Unadjusted					Adjusted*				
	10th	25th	50th	75th	90th	10th	25th	50th	75th	90th
No diabetes	-2.0	-1.6	-1.4	-1.2	-0.9	-1.9	-1.6	-1.4	-1.2	-1.0
Undiagnosed diabetes	-2.8	-2.2	-2.1	-1.9	-1.5	-2.5	-2.0	-1.9	-1.7	-1.4
Diagnosed diabetes	-3.7	-2.8	-2.8	-2.4	-2.0	-3.4	-2.5	-2.5	-2.2	-1.8

* Adjusted for the following characteristics at baseline and their interactions with time, continuous variables centered at their means: age (ref=54.67 years), sex (ref=male), race-center (ref=Forsyth County-White; Forsyth County-Black, Jackson-Black, Minneapolis-White, Washington County-White), systolic blood pressure (ref=121.22), hypertension medication use (ref=no; yes), body mass index (ref=27.68), HDL (ref=51.60), prevalent coronary heart disease (ref=no; yes), smoking status (ref=never; former, current), annual family income (ref: <$25,000; ≥$25,000), and educational status (ref: high school; less than high school, vocational school, college, graduate/professional school)

Abbreviations: *eGFR* estimated glomerular filtration rate

Legend: ·····No diabetes - - - -Undiagnosed diabetes ——— Diagnosed diabetes

Table B-1. Adjusted mean annual decline in eGFR by diabetes status without assignment of 15 ml/min/1.73m^2 at time of onset of end stage renal disease

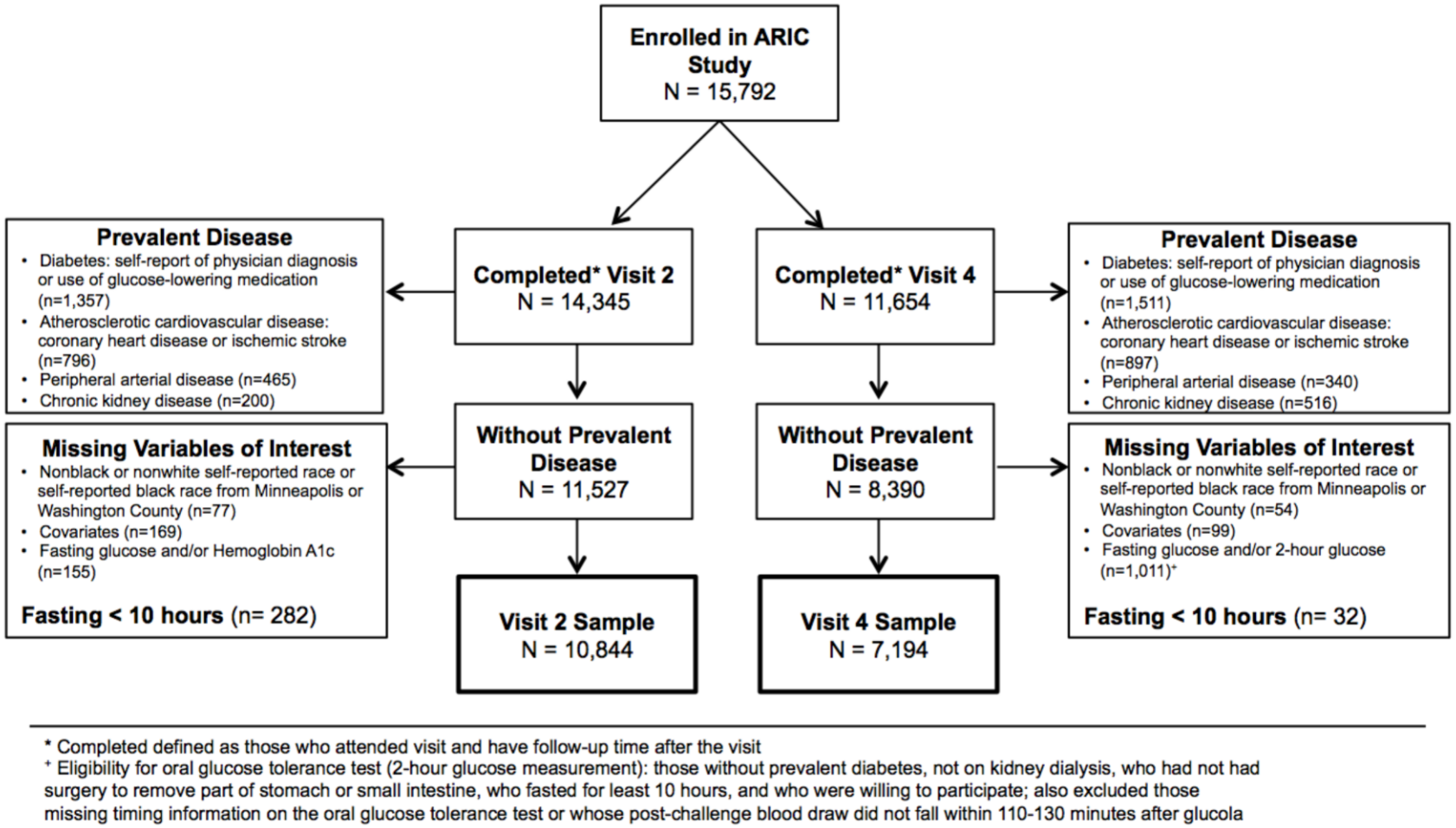
Diabetes status	Adjusted* mean annual decline in eGFR (ml/min/1.73m^2)	Difference from reference (REF)	*p*-value for difference
No diabetes	-1.4 (-1.5, -1.4)	0 (REF)	
Undiagnosed diabetes	-1.6 (-1.8, -1.5)	-0.2 (-0.3, -0.1)	0.005
Diagnosed diabetes	-2.0 (-2.2, -1.9)	-0.6 (-0.7, -0.5)	<0.001

* Adjusted for the following characteristics at baseline and their interactions with time, continuous variables centered at their means: age (ref=54.67 years), sex (ref=male), race-center (ref=Forsyth County-White; Forsyth County-Black, Jackson-Black, Minneapolis-White, Washington County-White), systolic blood pressure (ref=121.22), hypertension medication use (ref=no; yes), body mass index (ref=27.68), HDL (ref=51.60), prevalent coronary heart disease (ref=no; yes), smoking status (ref=never; former, current), annual family income (ref: <$25,000; ≥$25,000), and educational status (ref: high school; less than high school, vocational school, college, graduate/professional school)

Abbreviations: *eGFR* estimated glomerular filtration rate

Appendix C: Supplementary Materials for Chapter 2

Figure C-1. Participants included in the study



* Completed defined as those who attended visit and have follow-up time after the visit
+ Eligibility for oral glucose tolerance test (2-hour glucose measurement): those without prevalent diabetes, not on kidney dialysis, who had not had surgery to remove part of stomach or small intestine, who fasted for least 10 hours, and who were willing to participate; also excluded those missing timing information on the oral glucose tolerance test or whose post-challenge blood draw did not fall within 110-130 minutes after glucola

Table C-1. Baseline characteristics of ARIC participants without a history of cardiovascular disease, peripheral arterial disease, or diagnosed diabetes by clinical categories by different biomarkers of hyperglycemia*

	Normoglycemia	Prediabetes	Undiagnosed diabetes	Normoglycemia	Prediabetes	Undiagnosed diabetes
	WHO fasting glucose clinical categories			IEC HbA1c clinical categories		
Visit 2 (1990-92) N = 10,844	**<6.1 mmol/L n = 9,114**	**6.1-6.9 mmol/L n = 1,213**	**≥7.0 mmol/L n = 517**	**<42 mmol/mol n = 9,412**	**42-46 mmol/mol n = 970**	**≥48 mmol/mol n = 462**
Age (years)	57.0 (5.6)	58.1 (5.7)	57.7 (5.6)	56.9 (5.6)	58.4 (5.6)	58.1 (5.6)
Female, %	58.6	45.8	54.4	56.9	55.4	61.5
Black, %	19.2	29.8	37.3	17.1	47.8	49.8
Less than high school education, %	17.7	22.7	28.1	16.9	30.8	32.3
Body Mass Index (kg/m^2)	27.1 (5.0)	29.9 (5.3)	31.6 (6.1)	27.2 (4.9)	30.0 (5.8)	32.3 (6.3)
Obese (≥30 kg/m^2), %	22.8	41.8	54.4	23.1	43.3	59.5
Waist-to-hip ratio	0.91 (0.1)	0.95 (0.1)	0.97 (0.1)	0.91 (0.1)	0.95 (0.1)	0.97 (0.1)
Fasting glucose (mmol/L)	5.32 (0.4)	6.44 (0.2)	8.62 (2.5)	5.42 (0.5)	6.08 (0.8)	8.29 (2.91)
HbA1c (mmol/mol)	35.4 (4.3)	39.7 (5.3)	52.7 (17)	35.0 (3.5)	43.5 (1.5)	57.6 (16)
Hypercholesterolemia, %	76.1	84.4	87.6	76.4	84.5	87.9
Hypertension, %	27.7	45.8	54.6	28.1	47.9	53.9
Estimated glomerular filtration rate (mL/min/1.73 m^2)	97.1 (13)	97.1 (14)	99.7 (15)	96.9 (13)	98.5 (16)	101 (16)
Current smoker, %	21.5	22.1	19.7	20.7	28.0	23.6
Current drinker, %	60.6	56.5	54.2	62.0	47.9	41.8
Family history of diabetes, %	21.3	27.4	33.7	21.7	26.0	34.0

* Mean (SD) unless otherwise indicated

Abbreviations: HbA1c, hemoglobin A1c; IEC, International Expert Committee; WHO, World Health Organization

Table C-1., continued

	WHO fasting glucose clinical categories		
Visit 4 (1996-98) **N = 7,194**	**<6.1 mmol/L** **n = 6,241**	**6.1-6.9 mmol/L** **n = 621**	**≥7.0 mmol/L** **n = 332**
Age (years)	62.7 (5.5)	63.1 (5.5)	63.1 (5.4)
Female, %	59.7	45.1	51.8
Black, %	15.8	24.2	25.6
Less than high school education, %	14.4	20.9	23.2
Body Mass Index (kg/m^2)	27.9 (5.1)	31.1 (5.3)	32.1 (6.0)
Obese (≥30 kg/m^2), %	28.2	54.1	60.2
Waist-to-hip ratio	0.94 (0.1)	0.98 (0.1)	0.98 (0.1)
Fasting glucose (mmol/L)	5.26 (0.4)	6.45 (0.2)	8.72 (2.5)
2-hour glucose (mmol/L)	6.99 (2.1)	9.45 (2.7)	14.8 (4.3)
Hypercholesterolemia, %	75.5	85.4	87.7
Hypertension, %	38.4	53.5	60.5
Estimated glomerular filtration rate ($mL/min/1.73\ m^2$)	88.2 (12)	88.4 (13)	89.6 (12)
Current smoker, %	14.2	13.2	11.8
Current drinker, %	55.4	53.6	49.1
Family history of diabetes, %	21.2	28.0	33.1

* Mean (SD) unless otherwise indicated

Abbreviations: HbA1c, hemoglobin A1c; IEC, International Expert Committee; WHO, World Health Organization

Table C-2 (a-c). Cross-tabulation of participants by different clinical categories of prediabetes

a.) by ADA fasting glucose

		ADA fasting glucose			Total
		<5.6 mmol/L n=6,215	**5.6-6.9 mmol/L n=4,112**	**≥7.0 mmol/L n=517**	
Visit 2 (1990-92)					
WHO fasting glucose	**<6.1 mmol/L**	6,215	2,899	0	9,114
	6.1-6.9 mmol/L	0	1,213	0	1,213
	≥7.0 mmol/L‡	0	0	517	517
ADA HbA1c	**<39 mmol/mol**	5,496	2,802	57	8,355
	39-46 mmol/mol	701	1,161	165	2,027
	≥48 mmol/mol‡	18	149	295	462
IEC HbA1c	**<42 mmol/mol**	5,935	3,385	92	9,412
	42-46 mmol/mol	262	578	130	970
	≥48 mmol/mol‡	18	149	295	462
Visit 4 (1996-98)					
		ADA fasting glucose			**Total**
		<5.6 mmol/L n=4,720	**5.6-6.9 mmol/L n=2,142**	**≥7.0 mmol/L n=332**	
WHO fasting glucose	**<6.1 mmol/L**	4,720	1,521	0	6,241
	6.1-6.9 mmol/L	0	621	0	621
	> 7.0 mmol/L‡	0	0	332	332
ADA/WHO 2-hour glucose	**<7.8 mmol/L**	3,416	1,017	9	4,442
	7.8-11.0 mmol/L	1,152	814	43	2,009
	≥11.0 mmol/L‡	152	311	280	743

‡ Undiagnosed diabetes

Abbreviations: ADA, American Diabetes Association; HbA1c, hemoglobin A1c; IEC, International Expert Committee; WHO, World Health Organization

b.) by WHO fasting glucose

		WHO fasting glucose			Total
		<6.1 mmol/L n=9,114	6.1-6.9 mmol/L n=1,213	≥7.0 mmol/L n=517	
Visit 2 (1990-92)					
ADA HbA1c	**<39 mmol/mol**	7,693	605	57	8,355
	39-46 mmol/mol	1,359	503	165	2,027
	≥48 mmol/mol‡	62	105	295	462
IEC HbA1c	**< 42 mmol/mol**	8,501	819	92	9,412
	42-46 mmol/mol	551	289	130	970
	≥48 mmol/mol‡	62	105	295	462
Visit 4 (1996-98)					
		WHO fasting glucose			**Total**
		<6.1 mmol/L n=6,241	**6.1-6.9 mmol/L n=621**	**≥7.0 mmol/L n=332**	
ADA/WHO 2-hour glucose	**<7.8 mmol/L**	4,259	174	9	4,442
	7.8-11.0 mmol/L	1,691	275	43	2,009
	≥11.0 mmol/L‡	291	172	280	743

‡ Undiagnosed diabetes
Abbreviations: ADA, American Diabetes Association; HbA1c, hemoglobin A1c; IEC, International Expert Committee; WHO, World Health Organization

c.) by ADA HbA1c

		ADA HbA1c			Total
		<39 mmol/mol n=8,355	39-46 mmol/mol n=2,027	≥48 mmol/mol n=462	
Visit 2 (1990-92)					
IEC HbA1c	**<42 mmol/mol**	8,355	1,057	0	9,412
	42-46 mmol/mol	0	970	0	970
	≥48 mmol/mol‡	0	0	462	462

‡ Undiagnosed diabetes
Abbreviations: ADA, American Diabetes Association; HbA1c, hemoglobin A1c; IEC, International Expert Committee

Table C-3. Number of events and incidence rates per 1,000 person-years (95% confidence interval) for incident outcomes by different clinical categories of prediabetes and undiagnosed diabetes

Visit 2 (1990-92)		Incident diabetes		Chronic kidney disease		Atherosclerotic cardiovascular disease		Peripheral arterial disease		All-cause mortality	
		Events	IR (95% CI)	Events	IR (95% CI)	Events	IR (95% CI)	Events	IR (95% CI)	Events	IR (95% CI)
ADA fasting glucose definition	<5.6 mmol/L	1,080	9.37 (8.83, 9.95)	1,364	11.4 (10.8, 12.0)	746	6.23 (5.80, 6.69)	117	0.94 (0.79, 1.13)	1,618	13.0 (12.3, 13.6)
	5.6-6.9 mmol/L	1,638	25.3 (24.1, 26.6)	1,068	14.0 (13.2, 14.9)	676	8.98 (8.33, 9.68)	115	1.45 (1.21, 1.74)	1,341	16.7 (15.9, 17.6)
	≥7.0 mmol/L‡	434	109 (99.5, 120)	176	19.4 (16.8, 22.5)	134	15.1 (12.8, 17.9)	34	3.58 (2.56, 5.01)	218	22.5 (19.7, 25.7)
WHO fasting glucose definition	<6.1 mmol/L	2,041	12.5 (11.9, 13.0)	2,091	12.0 (11.5, 12.5)	1,209	6.97 (6.59, 7.37)	194	1.08 (0.93, 1.24)	2,505	13.8 (13.2, 14.3)
	6.1-6.9 mmol/L	677	41.5 (38.5, 44.7)	341	15.7 (14.1, 17.4)	213	9.87 (8.63, 11.3)	38	1.67 (1.21, 2.29)	454	19.6 (17.9, 21.5)
	≥7.0 mmol/L‡	434	109 (99.5, 120)	176	19.4 (16.8, 22.5)	134	15.1 (12.8, 17.9)	34	3.58 (2.56, 5.01)	218	22.5 (19.7, 25.7)
ADA HbA1c definition	<39 mmol/mol	1,783	11.7 (11.2, 12.3)	1,859	11.5 (11.0, 12.0)	1,009	6.26 (5.89, 6.66)	158	0.95 (0.81, 1.11)	2,149	12.8 (12.2, 13.3)
	39-46 mmol/mol	974	34.3 (32.2, 36.5)	581	16.2 (14.9, 17.6)	423	12.0 (10.9, 13.2)	68	1.81 (1.43, 2.30)	817	21.5 (20.1, 23.0)
	≥48 mmol/mol‡	395	121 (110, 134)	168	21.3 (18.3, 24.8)	124	16.2 (13.5, 19.3)	40	4.85 (3.55, 6.61)	211	24.8 (21.7, 28.4)
IEC HbA1c definition	<42 mmol/mol	2,210	13.1 (12.6, 13.7)	2,147	11.9 (11.4, 12.4)	1,197	6.66 (6.29, 7.04)	190	1.02 (0.88, 1.17)	2,542	13.5 (13.0, 14.0)
	42-46 mmol/mol	547	44.2 (40.7, 48.1)	293	17.3 (15.4, 19.4)	235	14.3 (12.5, 16.2)	36	2.03 (1.47, 2.82)	424	23.6 (21.5, 26.0)
	≥48 mmol/mol‡	395	121 (110, 134)	168	21.3 (18.3, 24.8)	124	16.2 (13.5, 19.3)	40	4.85 (3.55, 6.61)	211	24.8 (21.7, 28.4)

‡ Undiagnosed diabetes; Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; IEC, International Expert Committee; IR, incidence rate; WHO, World Health Organization

Table C-3., continued

Visit 4 (1996-98)		Incident diabetes		Chronic kidney disease		Atherosclerotic cardiovascular disease		Peripheral arterial disease		All-cause mortality	
		Events	IR (95% CI)	Events	IR (95% CI)	Events	IR (95% CI)	Events	IR (95% CI)	Events	IR (95% CI)
ADA fasting glucose definition	<5.6 mmol/L	698	10.8 (10.0, 11.6)	907	13.2 (12.3, 14.0)	435	6.34 (5.77, 6.96)	67	0.95 (0.75, 1.20)	938	13.2 (12.4, 14.0)
	5.6-6.9 mmol/L	869	35.7 (33.4, 38.1)	453	14.8 (13.5, 16.2)	269	8.88 (7.88, 10.0)	38	1.20 (0.88, 1.66)	523	16.5 (15.1, 17.9)
	≥7.0 mmol/L‡	292	198 (176, 222)	84	18.8 (15.2, 23.3)	56	12.6 (9.70, 16.4)	10	2.16 (1.16, 4.02)	107	22.9 (19.0, 27.7)
WHO fasting glucose definition	<6.1 mmol/L	1,208	14.5 (13.7, 15.4)	1,211	13.3 (12.6, 14.1)	627	6.95 (6.43, 7.51)	98	1.05 (0.86, 1.28)	1,283	13.7 (12.9, 14.4)
	6.1-6.9 mmol/L	359	61.4 (55.3, 68.0)	149	17.1 (14.6, 20.1)	77	8.86 (7.09, 11.1)	7	0.77 (0.37, 1.62)	178	19.6 (16.9, 22.7)
	≥7.0 mmol/L‡	292	198 (176, 222)	84	18.8 (15.2, 23.3)	56	12.6 (9.70, 16.4)	10	2.16 (1.16, 4.02)	107	22.9 (19.0, 27.7)
ADA/WHO 2-hour glucose definition	<7.8 mmol/L	686	11.3 (10.5, 12.1)	827	12.7 (11.9, 13.6)	431	6.67 (6.07, 7.33)	75	1.13 (0.90, 1.41)	861	12.8 (12.0, 13.7)
	7.8-11.0 mmol/L	645	26.7 (24.7, 28.8)	429	14.9 (13.6, 16.4)	217	7.61 (6.66, 8.69)	28	0.95 (0.65, 1.37)	491	16.5 (15.1, 18.0)
	≥11.0 mmol/L‡	528	98.2 (90.2, 107)	188	18.3 (15.9, 21.1)	112	10.9 (9.09, 13.2)	12	1.13 (0.64, 1.98)	216	20.1 (17.6, 23.0)

‡ Undiagnosed diabetes; Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; IEC, International Expert Committee; IR, incidence rate; WHO, World Health Organization

Table C-4. Fully adjusted hazard ratios and Harrell's C-statistic (95% confidence intervals) for incident outcomes by different clinical categories of prediabetes and undiagnosed diabetes

Visit 2 (1990-92)		Incident diabetes	Chronic kidney disease	Atherosclerotic cardiovascular disease	Peripheral arterial disease	All-cause mortality
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	2.26 (2.08, 2.45)*	1.04 (0.95, 1.13)	1.07 (0.96, 1.20)	1.15 (0.87, 1.50)	1.05 (0.97, 1.13)
	≥7.0 mmol/L‡	12.4 (11.0, 14.0)*	1.41 (1.19, 1.66)*	1.56 (1.28, 1.90)*	2.48 (1.64, 3.77)*	1.35 (1.16, 1.57)*
	C-statistic (95% CI)	0.762 (0.753, 0.770)	0.693 (0.682, 0.703)	0.709 (0.696, 0.721)	0.794 (0.768, 0.819)	0.720 (0.711, 0.729)
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	2.85 (2.60, 3.12)*	1.11 (0.98, 1.24)	1.02 (0.88, 1.18)	1.12 (0.78, 1.59)	1.12 (1.01, 1.24)*
	≥7.0 mmol/L‡	9.77 (8.71, 11.0)*	1.40 (1.20, 1.65)*	1.50 (1.25, 1.81)*	2.35 (1.59, 3.47)*	1.35 (1.17, 1.56)*
	C-statistic (95% CI)	0.761 (0.752, 0.769)	0.693 (0.683, 0.703)	0.708 (0.696, 0.721)	0.794 (0.768, 0.819)	0.720 (0.711, 0.729)
ADA HbA1c definition	<39 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	39-46 mmol/mol	2.71 (2.45, 2.95)*	1.27 (1.15, 1.40)*	1.40 (1.24, 1.58)*	1.39 (1.02, 1.87)*	1.31 (1.21, 1.43)*
	≥48 mmol/mol‡	13.6 (12.0, 15.4)*	1.69 (1.43, 2.01)*	1.78 (1.45, 2.17)*	3.86 (2.62, 5.69)*	1.56 (1.34, 1.82)*
	C-statistic (95% CI)	0.760 (0.751, 0.769)	0.694 (0.684, 0.704)	0.711 (0.699, 0.724)	0.800 (0.774, 0.825)	0.722 (0.713, 0.731)
IEC HbA1c definition	<42 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	42-46 mmol/mol	3.14 (2.83, 3.47)*	1.31 (1.15, 1.49)*	1.53 (1.32, 1.78)*	1.45 (0.99, 2.11)	1.35 (1.21, 1.51)*
	≥48 mmol/mol‡	11.8 (10.5, 13.4)*	1.64 (1.39, 1.94)*	1.72 (1.41, 2.09)*	3.69 (2.53, 5.39)*	1.50 (1.30, 1.75)*
	C-statistic (95% CI)	0.753 (0.744, 0.762)	0.694 (0.684, 0.704)	0.711 (0.698, 0.723)	0.799 (0.774, 0.825)	0.722 (0.713, 0.730)

Adjusted for age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC), education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

‡ Undiagnosed diabetes; * $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-4., continued

Visit 4 (1996-98)		Incident diabetes	Chronic kidney disease	Atherosclerotic cardiovascular disease	Peripheral arterial disease	All-cause mortality
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	2.78 (2.51, 3.09)*	0.91 (0.81, 1.03)	1.10 (0.94, 1.29)	0.99 (0.65, 1.51)	1.13 (1.01, 1.26)*
	≥7.0 mmol/L‡	15.6 (13.3, 18.2)*	1.10 (0.87, 1.39)	1.39 (1.03, 1.86)*	1.76 (0.87, 3.57)	1.68 (1.36, 2.08)*
	C-statistic (95% CI)	0.769 (0.757, 0.780)	0.684 (0.670, 0.698)	0.698 (0.679, 0.716)	0.807 (0.765, 0.848)	0.714 (0.702, 0.727)
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	3.50 (3.10, 3.96)*	1.05 (0.88, 1.26)	0.97 (0.76, 1.23)	0.58 (0.27, 1.26)	1.29 (1.09, 1.51)*
	≥7.0 mmol/L‡	11.6 (10.0, 13.4)*	1.16 (0.92, 1.46)	1.32 (0.99, 1.75)	1.66 (0.84, 3.27)	1.66 (1.35, 2.04)*
	C-statistic (95% CI)	0.762 (0.751, 0.774)	0.684 (0.670, 0.698)	0.697 (0.679, 0.716)	0.809 (0.768, 0.851)	0.715 (0.702, 0.727)
ADA / WHO 2-hour glucose definition	<7.8 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	7.8-11.0 mmol/L	2.07 (1.85, 2.31)*	1.07 (0.95, 1.21)	0.98 (0.82, 1.16)	0.83 (0.53, 1.31)	1.18 (1.05, 1.33)*
	≥11.0 mmol/L‡	7.61 (6.72, 8.61)*	1.17 (0.99, 1.39)	1.19 (0.95, 1.48)	0.87 (0.46, 1.65)	1.33 (1.14, 1.56)*
	C-statistic (95% CI)	0.768 (0.757, 0.779)	0.684 (0.670, 0.698)	0.698 (0.679, 0.716)	0.806 (0.765, 0.847)	0.714 (0.701, 0.726)

Adjusted for age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC), education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-5. Difference in Harrell's C-statistic (95% confidence interval) to assess discrimination of models with clinical categories‡ for risk future clinical outcomes

Visit 2 (1990-92)		Incident diabetes	Chronic kidney disease	Atherosclerotic cardiovascular disease	Peripheral arterial disease	All-cause mortality
Demographic adjusted	ADA fasting glucose-WHO fasting glucose	0.020 (0.012, 0.028)*	-0.001 (-0.003, 0.001)	0.002 (-0.000, 0.005)	0.001 (-0.005, 0.008)	-0.000 (-0.001, 0.001)
	ADA fasting glucose-ADA HbA1c	0.020 (0.010, 0.030)*	-0.005 (-0.008, -0.001)*	-0.010 (-0.016, -0.004)*	-0.020 (-0.034, -0.006)*	-0.005 (-0.007, -0.003)*
	ADA fasting glucose-IEC HbA1c	0.044 (0.034, 0.054)*	-0.003 (-0.006, 0.000)	-0.006 (-0.012, -0.001)*	-0.017 (-0.029, -0.004)*	-0.004 (-0.006, -0.002)*
	WHO fasting glucose-ADA HbA1c	0.000 (-0.009, 0.009)	-0.004 (-0.008, -0.000)*	-0.012 (-0.018, -0.007)*	-0.022 (-0.036, -0.008)*	-0.005 (-0.007, -0.002)*
	WHO fasting glucose-IEC HbA1c	0.024 (0.015, 0.033)*	-0.002 (-0.006, 0.001)	-0.009 (-0.014, -0.004)*	-0.018 (-0.030, -0.006)*	-0.003 (-0.005, -0.001)*
	ADA HbA1c-IEC HbA1c	0.024 (0.018, 0.030)*	0.002 (-0.001, 0.004)	0.004 (-0.001, 0.008)	0.004 (-0.005, 0.013)	0.001 (-0.001, 0.003)

‡ Clinical categories refer to normoglycemia, prediabetes, and undiagnosed diabetes

Demographic adjusted included age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

Fully adjusted included Demographic adjusted + education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; HbA1c, hemoglobin A1c; IEC, International Expert Committee; WHO, World Health Organization

Table C-5., continued

Visit 2 (1990-92)		Incident diabetes	Chronic kidney disease	Atherosclerotic cardiovascular disease	Peripheral arterial disease	All-cause mortality
Fully adjusted	ADA fasting glucose-WHO fasting glucose	0.001 (-0.004, 0.005)	-0.000 (-0.001, 0.000)	0.000 (-0.000, 0.001)	-0.000 (-0.002, 0.001)	0.000 (-0.001, 0.000)
	ADA fasting glucose-ADA HbA1c	0.002 (-0.004, 0.008)	-0.001 (-0.003, 0.000)	-0.002 (-0.005, 0.000)	-0.006 (-0.011, -0.001)*	-0.002 (-0.003, -0.001)*
	ADA fasting glucose-IEC HbA1c	0.009 (0.003, 0.014)*	-0.001 (-0.003, 0.000)	-0.002 (-0.005, 0.001)	-0.006 (-0.010, -0.001)*	-0.002 (-0.003, -0.001)*
	WHO fasting glucose-ADA HbA1c	0.001 (-0.005, 0.006)	-0.001 (-0.003, 0.001)	-0.003 (-0.005, 0.000)	-0.006 (-0.011, -0.001)*	-0.002 (-0.003, -0.000)*
	WHO fasting glucose-IEC HbA1c	0.008 (0.003, 0.013)*	-0.001 (-0.003, 0.000)	-0.002 (-0.005, 0.000)	-0.006 (-0.010, -0.001)*	-0.002 (-0.003, -0.000)*
	ADA HbA1c-IEC HbA1c	0.007 (0.003, 0.011)*	0.000 (-0.001, 0.001)	0.000 (-0.002, 0.003)	0.000 (-0.002, 0.003)	0.000 (-0.001, 0.001)

‡ Clinical categories refer to normoglycemia, prediabetes, and undiagnosed diabetes

Demographic adjusted included age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

Fully adjusted included Demographic adjusted + education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; HbA1c, hemoglobin A1c; IEC, International Expert Committee; WHO, World Health Organization

Table C-5., continued

Visit 4 (1996-98)		Incident diabetes	Chronic kidney disease	Atherosclerotic cardiovascular disease	Peripheral arterial disease	All-cause mortality
Demographic adjusted	ADA fasting glucose-WHO fasting glucose	0.032 (0.022, 0.041)*	-0.001 (-0.002, 0.001)	0.002 (-0.001, 0.006)	-0.003 (-0.011, 0.005)	-0.001 (-0.002, 0.001)
	ADA fasting glucose-ADA/WHO 2-hour glucose	-0.002 (-0.015, 0.010)	-0.001 (-0.005, 0.002)	0.001 (-0.003, 0.006)	0.002 (-0.010, 0.015)	0.001 (-0.001, 0.003)
	WHO fasting glucose-ADA/WHO 2-hour glucose	-0.034 (-0.047, -0.021)*	-0.001 (-0.004, 0.003)	-0.001 (-0.004, 0.003)	0.005 (-0.008, 0.018)	0.002 (-0.001, 0.004)
Fully adjusted	ADA fasting glucose-WHO fasting glucose	0.006 (-0.000, 0.013)	0.000 (-0.001, 0.001)	0.000 (-0.001, 0.002)	-0.003 (-0.007, 0.002)	-0.000 (-0.002, 0.001)
	ADA fasting glucose-ADA/WHO 2-hour glucose	0.001 (-0.008, 0.009)	-0.000 (-0.002, 0.001)	-0.000 (-0.002, 0.002)	0.001 (-0.006, 0.007)	0.001 (-0.001, 0.003)
	WHO fasting glucose-ADA/WHO 2-hour glucose	-0.006 (-0.013, 0.002)	-0.000 (-0.001, 0.001)	-0.001 (-0.002, 0.001)	0.003 (-0.004, 0.011)	0.001 (-0.001, 0.003)

‡ Clinical categories refer to normoglycemia, prediabetes, and undiagnosed diabetes

Demographic adjusted included age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

Fully adjusted included Demographic adjusted + education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; HbA1c, hemoglobin A1c; IEC, International Expert Committee; WHO, World Health Organization

Table C-6. Net reclassification index† (95% confidence intervals) for 10-year risk of incident outcomes by different clinical categories‡ of prediabetes and undiagnosed diabetes compared to ADA fasting glucose

Visit 2 (1990-92)		Incident diabetes			Chronic kidney disease			Atherosclerotic cardiovascular disease		
		Overall	Event	Non-event	Overall	Event	Non-event	Overall	Event	Non-event
Demo-graphic adjusted	ADA fasting glucose definition	Ref			Ref			Ref		
	WHO fasting glucose definition	-0.264 (-0.306, -0.218)*	0.177 (0.143, 0.222)*	-0.440 (-0.456, -0.421)*	-0.042 (-0.159, 0.055)	0.362 (0.240, 0.453)*	-0.404 (-0.415, -0.390)*	-0.073 (-0.140, -0.010)*	0.336 (0.263, 0.376)*	-0.409 (-0.425, -0.391)*
	ADA HbA1c definition	-0.089 (-0.150, -0.028)*	0.238 (0.175, 0.286)*	-0.328 (-0.345, -0.307)*	0.056 (-0.006, 0.172)	-0.060 (-0.122, 0.057)*	0.116 (0.104, 0.139)*	0.140 (0.090, 0.279)*	-0.047 (-0.095, 0.006)	0.187 (0.172, 0.204)*
	IEC HbA1c definition	-0.252 (-0.318, -0.178)*	0.081 (0.021, 0.130)*	-0.333 (-0.345, -0.311)*	-0.028 (-0.090, 0.074)	0.134 (0.048, 0.243)*	-0.163 (-0.186, -0.147)*	-0.010 (-0.060, 0.071)	0.117 (0.090, 0.189)*	-0.127 (-0.148, -0.107)*
Fully adjusted	ADA fasting glucose definition	Ref			Ref			Ref		
	WHO fasting glucose definition	-0.171 (-0.210, -0.121)*	0.265 (0.230, 0.309)*	-0.437 (-0.452, -0.418)*	-0.105 (-0.189, 0.029)	0.187 (0.084, 0.315)*	-0.292 (-0.309, -0.270)*	-0.135 (-0.199, -0.072)*	0.059 (-0.000, 0.117)	-0.193 (-0.211, -0.178)*
	ADA HbA1c definition	-0.021 (-0.119, 0.041)	0.223 (0.141, 0.274)*	-0.244 (-0.260, -0.228)*	0.206 (0.128, 0.314)*	-0.188 (-0.261, -0.085)*	0.394 (0.382, 0.402)*	0.111 (0.053, 0.227)*	-0.200 (-0.252, -0.082)*	0.311 (0.282, 0.323)*
	IEC HbA1c definition	-0.179 (-0.252, -0.116)*	0.086 (0.031, 0.128)*	-0.265 (-0.284, -0.240)*	-0.033 (-0.146, 0.048)	-0.372 (-0.485, -0.282)*	0.339 (-0.333, 0.354)	-0.074 (-0.110, 0.007)	-0.281 (-0.306, -0.205)*	0.206 (0.194, 0.226)*

‡ Clinical categories refer to normoglycemia, prediabetes, and undiagnosed diabetes

Demographic adjusted included age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

Fully adjusted included Demographic adjusted + education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; IEC, International Expert Committee; HbA1c, hemoglobin A1c; WHO, World Health Organization

Table C-6., continued

Visit 2 (1990-92)		Peripheral arterial disease			All-cause mortality		
		Overall	Event	Non-event	Overall	Event	Non-event
Demographic adjusted	ADA fasting glucose definition	Ref			Ref		
	WHO fasting glucose definition	-0.212 (-0.330, -0.059)*	0.194 (0.073, 0.352)*	-0.401 (-0.415, -0.389)*	-0.072 (-0.119, -0.027)*	0.335 (0.290, 0.380)*	-0.407 (-0.419, -0.392)*
	ADA HbA1c definition	0.256 (0.191, 0.363)*	-0.070 (-0.144, 0.046)	0.326 (0.316, 0.335)*	0.225 (0.172, 0.295)*	-0.342 (-0.392, -0.278)*	0.567 (0.548, 0.580)*
	IEC HbA1c definition	0.035 (-0.167, 0.172)	0.070 (-0.130, 0.275)	-0.036 (-0.053, -0.010)*	-0.044 (-0.106, 0.031)	-0.020 (-0.060, 0.064)	-0.024 (-0.046, -0.000)*
Fully adjusted	ADA fasting glucose definition	Ref			Ref		
	WHO fasting glucose definition	-0.191 (-0.334, -0.019)*	0.218 (0.084, 0.400)*	-0.409 (-0.423, -0.395)*	-0.156 (-0.208, -0.092)*	0.157 (0.098, 0.196)*	-0.313 (-0.330, -0.294)*
	ADA HbA1c definition	0.089 (0.020, 0.245)*	-0.099 (-0.231, 0.060)	0.188 (0.176, 0.196)*	0.089 (0.015, 0.145)*	-0.295 (-0.373, 0.233)	0.384 (0.364, 0.399)*
	IEC HbA1c definition	0.023 (-0.159, 0.244)	-0.125 (-0.311, 0.101)	0.148 (0.126, 0.160)*	-0.102 (-0.184, -0.033)*	-0.357 (-0.430, -0.293)*	0.255 (0.237, 0.265)*

‡ Clinical categories refer to normoglycemia, prediabetes, and undiagnosed diabetes

Demographic adjusted included age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

Fully adjusted included Demographic adjusted + education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; IEC, International Expert Committee; HbA1c, hemoglobin A1c; WHO, World Health Organization

Table C-6., continued

Visit 4 (1996-98)		Incident diabetes			Chronic kidney disease			Atherosclerotic cardiovascular disease		
		Overall	Event	Non-event	Overall	Event	Non-event	Overall	Event	Non-event
Demo-graphic adjusted	ADA fasting glucose definition	Ref			Ref			Ref		
	WHO fasting glucose definition	-0.326 (-0.366, -0.288)*	0.264 (0.193, 0.303)*	-0.590 (-0.607, -0.579)*	-0.059 (-0.134, 0.022)	0.367 (0.295, 0.433)*	-0.426 (-0.442, -0.403)*	-0.139 (-0.259, -0.038)*	0.226 (0.124, 0.332)*	-0.365 (-0.396, -0.349)*
	ADA / WHO 2- hour glucose definition	-0.199 (-0.244, -0.139)*	-0.207 (-0.249, -0.152)*	0.008 (-0.004, 0.031)	0.027 (-0.078, 0.101)	-0.285 (-0.382, -0.218)*	0.312 (0.275, 0.330)*	-0.113 (-0.210, -0.016)*	0.210 (0.123, 0.314)*	-0.323 (-0.336, -0.305)*
Fully adjusted	ADA fasting glucose definition	Ref			Ref			Ref		
	WHO fasting glucose definition	-0.351 (-0.391, -0.308)*	0.238 (0.166, 0.271)*	-0.589 (-0.604, -0.577)*	-0.015 (-0.126, 0.103)	-0.280 (-0.371, -0.223)*	0.265 (0.245, 0.275)*	-0.112 (-0.218, -0.025)*	0.183 (0.094, 0.244)*	-0.295 (-0.329, -0.280)*
	ADA / WHO 2- hour glucose definition	-0.164 (-0.214, -0.124)*	-0.187 (-0.249, -0.145)*	0.024 (0.004, 0.036)*	-0.023 (-0.080, 0.061)	-0.173 (-0.244, -0.104)*	0.150 (0.132, 0.173)*	-0.068 (-0.178, -0.003)*	0.118 (0.023, 0.193)*	-0.186 (-0.210, -0.162)*

‡ Clinical categories refer to normoglycemia, prediabetes, and undiagnosed diabetes

Demographic adjusted included age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

Fully adjusted included Demographic adjusted + education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; IEC, International Expert Committee; HbA1c, hemoglobin A1c; WHO, World Health Organization

Table C-6., continued

Visit 4 (1996-98)		Peripheral arterial disease			All-cause mortality		
		Overall	Event	Non-event	Overall	Event	Non-event
Demo-graphic adjusted	ADA fasting glucose definition	-0.156 (-0.313, 0.055)	0.223 (0.060, 0.429)*	-0.379 (-0.393, -0.368)*	-0.037 (-0.137, 0.009)	0.494 (0.415, 0.543)*	-0.531 (-0.552, -0.514)*
	WHO fasting glucose definition	-0.127 (-0.428 (0.044)	0.150 (-0.149, 0.303)	-0.277 (-0.286, -0.257)*	-0.030 (-0.134, 0.045)	-0.051 (-0.147, -0.016)*	0.022 (-0.007, 0.044)
	ADA / WHO 2- hour glucose definition	-0.156 (-0.313, 0.055)	0.223 (0.060, 0.429)*	-0.379 (-0.393, -0.368)*	-0.037 (-0.137, 0.009)	0.494 (0.415, 0.543)*	-0.531 (-0.552, -0.514)*
Fully adjusted	ADA fasting glucose definition	0.084 (-0.021, 0.292)	0.639 (0.536, 0.846)*	-0.555 (-0.569, -0.530)*	-0.025 (-0.109, 0.008)	0.506 (0.425, 0.538)*	-0.531 (-0.547, -0.515)*
	WHO fasting glucose definition	-0.129 (-0.498, 0.062)	0.152 (-0.207, 0.333)	-0.281 (-0.294, -0.254)*	-0.010 (-0.131, 0.095)	-0.064 (-0.162, 0.032)	0.053 (0.031, 0.069)*
	ADA / WHO 2- hour glucose definition	0.084 (-0.021, 0.292)	0.639 (0.536, 0.846)*	-0.555 (-0.569, -0.530)*	-0.025 (-0.109, 0.008)	0.506 (0.425, 0.538)*	-0.531 (-0.547, -0.515)*

‡ Clinical categories refer to normoglycemia, prediabetes, and undiagnosed diabetes

Demographic adjusted included age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

Fully adjusted included Demographic adjusted + education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; IEC, International Expert Committee; HbA1c, hemoglobin A1c; WHO, World Health Organization

Table C-7. Demographic adjusted hazard ratio and Harrell's C-statistic (95% confidence intervals) for incident outcomes by different clinical categories of prediabetes, excluding undiagnosed diabetes

Visit 2 (1990-92)		Incident diabetes	Chronic kidney disease	Atherosclerotic cardiovascular disease	Peripheral arterial disease	All-cause mortality
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	2.92 (2.70, 3.16)*	1.17 (1.08, 1.27)*	1.23 (1.11, 1.37)*	1.30 (1.00, 1.69)*	1.12 (1.04, 1.20)*
	C-statistic (95% CI)	0.668 (0.658, 0.678)	0.633 (0.621, 0.644)	0.658 (0.643, 0.672)	0.690 (0.656, 0.724)	0.683 (0.673, 0.693)
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	3.85 (3.52, 4.21)*	1.28 (1.14, 1.43)*	1.21 (1.05, 1.41)*	1.32 (0.93, 1.87)	1.24 (1.12, 1.37)*
	C-statistic (95% CI)	0.644 (0.633, 0.655)	0.634 (0.622, 0.645)	0.655 (0.641, 0.669)	0.688 (0.654, 0.723)	0.683 (0.674, 0.693)
ADA HbA1c definition	<39 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	39-46 mmol/mol	3.40 (3.13, 3.70)*	1.41 (1.28, 1.56)*	1.70 (1.51, 1.92)*	1.75 (1.30, 2.35)*	1.49 (1.37, 1.62)*
	C-statistic (95% CI)	0.648 (0.637, 0.659)	0.636 (0.624, 0.647)	0.666 (0.652, 0.680)	0.703 (0.668, 0.738)	0.687 (0.677, 0.696)
IEC HbA1c definition	<42 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	42-46 mmol/mol	4.11 (3.71, 4.55)*	1.48 (1.31, 1.69)*	1.91 (1.65, 2.21)*	1.83 (1.26, 2.66)*	1.55 (1.39, 1.73)*
	C-statistic (95% CI)	0.620 (0.609, 0.631)	0.634 (0.623, 0.645)	0.662 (0.648, 0.676)	0.698 (0.663, 0.733)	0.686 (0.676, 0.695)

Adjusted for age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-7., continued

Visit 4 (1996-98)		Incident diabetes	Chronic kidney disease	Atherosclerotic cardiovascular disease	Peripheral arterial disease	All-cause mortality
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	3.47 (3.13, 3.84)*	1.07 (0.96, 1.20)	1.24 (1.06, 1.45)*	1.08 (0.72, 1.62)	1.14 (1.02, 1.27)*
	C-statistic (95% CI)	0.677 (0.663, 0.690)	0.623 (0.608, 0.638)	0.656 (0.636, 0.677)	0.701 (0.651, 0.751)	0.685 (0.671, 0.698)
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	4.55 (4.03, 5.13)*	1.23 (1.04, 1.46)*	1.10 (0.86, 1.39)	0.62 (0.29, 1.35)	1.29 (1.10, 1.51)*
	C-statistic (95% CI)	0.637 (0.623, 0.652)	0.624 (0.608, 0.639)	0.654 (0.633, 0.674)	0.704 (0.654, 0.754)	0.685 (0.672, 0.699)
ADA / WHO 2-hour glucose	<7.8 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	7.8-11.0 mmol/L	2.58 (2.31, 2.88)*	1.16 (1.03, 1.31)*	1.09 (0.92, 1.28)	0.82 (0.53, 1.27)	1.18 (1.05, 1.32)*
	C-statistic (95% CI)	0.652 (0.637, 0.668)	0.624 (0.608, 0.640)	0.658 (0.636, 0.679)	0.705 (0.654, 0.756)	0.684 (0.670, 0.698)

Adjusted for age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-8. Fully adjusted hazard ratio and Harrell's C-statistic (95% confidence intervals) for incident outcomes by different clinical categories of prediabetes, excluding undiagnosed diabetes

Visit 2 (1990-92)		Incident diabetes	Chronic kidney disease	Atherosclerotic cardiovascular disease	Peripheral arterial disease	All-cause mortality
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	2.26 (2.08, 2.45)*	1.04 (0.96, 1.13)	1.08 (0.97, 1.21)	1.14 (0.87, 1.50)	1.04 (0.96, 1.12)
	C-statistic (95% CI)	0.727 (0.717, 0.736)	0.692 (0.681, 0.703)	0.707 (0.693, 0.720)	0.793 (0.765, 0.821)	0.720 (0.711, 0.730)
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	2.85 (2.60, 3.12)*	1.11 (0.99, 1.25)	1.02 (0.88, 1.19)	1.11 (0.78, 1.59)	1.12 (1.01, 1.24)*
	C-statistic (95% CI)	0.726 (0.717, 0.736)	0.692 (0.682, 0.703)	0.706 (0.693, 0.720)	0.793 (0.765, 0.821)	0.721 (0.712, 0.730)
ADA HbA1c definition	<39 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	39-46 mmol/mol	2.71 (2.48, 2.95)*	1.26 (1.14, 1.39)*	1.41 (1.25, 1.60)*	1.35 (1.00, 1.83)	1.31 (1.20, 1.43)*
	C-statistic (95% CI)	0.726 (0.717, 0.736)	0.692 (0.681, 0.703)	0.709 (0.696, 0.722)	0.794 (0.766, 0.823)	0.722 (0.713, 0.731)
IEC HbA1c definition	<42 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	42-46 mmol/mol	3.12 (2.81, 3.46)*	1.29 (1.13, 1.47)*	1.55 (1.33, 1.80)*	1.41 (0.96, 2.06)	1.34 (1.20, 1.50)*
	C-statistic (95% CI)	0.719 (0.709, 0.728)	0.692 (0.681, 0.703)	0.708 (0.695, 0.721)	0.794 (0.766, 0.822)	0.722 (0.712, 0.731)

Adjusted for age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC), education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-8., continued

Visit 4 (1996-98)		Incident diabetes	Chronic kidney disease	Atherosclerotic cardiovascular disease	Peripheral arterial disease	All-cause mortality
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	2.70 (2.43, 3.00)*	0.92 (0.82, 1.04)	1.10 (0.94, 1.30)	1.00 (0.65, 1.52)	1.12 (1.00, 1.26)
	C-statistic (95% CI)	0.730 (0.717, 0.742)	0.682 (0.668, 0.697)	0.694 (0.675, 0.713)	0.805 (0.761, 0.849)	0.713 (0.700, 0.726)
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	3.41 (3.01, 3.85)*	1.07 (0.89, 1.27)	0.97 (0.76, 1.24)	0.59 (0.27, 1.28)	1.28 (1.09, 1.51)*
	C-statistic (95% CI)	0.722 (0.709, 0.735)	0.682 (0.668, 0.697)	0.694 (0.674, 0.713)	0.808 (0.764, 0.851)	0.714 (0.700, 0.727)
ADA / WHO 2-hour glucose	<7.8 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	7.8-11.0 mmol/L	2.06 (1.84, 2.31)*	1.09 (0.96, 1.23)	1.00 (0.84, 1.18)	0.82 (0.52, 1.30)	1.20 (1.07, 1.35)*
	C-statistic (95% CI)	0.711 (0.697, 0.725)	0.693 (0.668, 0.698)	0.696 (0.675, 0.716)	0.807 (0.764, 0.850)	0.714 (0.700, 0.728)

Adjusted for age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC), education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-9. Demographic adjusted hazard ratios (95% CI) and p-values for interaction for incident outcomes by different clinical categories of prediabetes and undiagnosed diabetes, by race (visit 2: black N=2,299, white N=8,545; visit 4: black N=1,221, white N=5,973)

Visit 2 (1990-92)		Incident diabetes		Chronic kidney disease		Atherosclerotic cardiovascular disease	
		Black	White	Black	White	Black	White
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	2.42 (2.07, 2.82)*	3.10 (2.83, 3.39)*	1.05 (0.88, 1.24)	1.21 (1.11, 1.33)*	1.15 (0.93, 1.43)	1.28 (1.13, 1.44)*
	≥7.0 mmol/L‡	14.2 (11.6, 17.4)*	22.2 (19.3, 25.6)*	1.73 (1.33, 2.24)*	1.75 (1.43, 2.15)*	2.08 (1.52, 2.84)*	2.12 (1.68, 2.68)*
	p-value	0.0052		0.32		0.73	
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	3.18 (2.71, 3.73)*	4.04 (3.63, 4.49)*	1.06 (0.85, 1.33)	1.37 (1.20, 1.57)*	1.08 (0.82, 1.43)	1.28 (1.07, 1.52)*
	≥7.0 mmol/L‡	11.2 (9.31, 13.4)*	16.0 (14.0, 18.3)*	1.71 (1.33, 2.19)*	1.68 (1.37, 2.05)*	1.96 (1.45, 2.64)*	1.96 (1.57, 2.46)*
	p-value	0.007		0.14		0.61	

Adjusted for age, sex (male, female)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-9., continued

Visit 2 (1990-92)		Incident diabetes		Chronic kidney disease		Atherosclerotic cardiovascular disease	
		Black	White	Black	White	Black	White
ADA HbA1c definition	<39 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	39-46 mmol/mol	2.53 (2.18, 2.94)*	3.80 (3.45, 4.19)*	1.34 (1.13, 1.59)*	1.45 (1.29, 1.63)*	1.51 (1.22, 1.89)*	1.81 (1.57, 2.08)*
	≥48 mmol/mol‡	14.1 (11.6, 17.0)*	26.4 (22.6, 30.8)*	1.73 (1.34, 2.23)*	2.36 (1.91, 2.91)*	2.43 (1.81, 3.26)*	2.31 (1.78, 2.99)*
	p-value	< 0.0001		0.15		0.31	
IEC HbA1c definition	<42 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	42-46 mmol/mol	2.95 (2.53, 3.45)*	4.99 (4.40, 5.66)*	1.29 (1.06, 1.58)*	1.68 (1.42, 1.98)*	1.72 (1.36, 2.17)*	2.08 (1.72, 2.50)*
	≥48 mmol/mol‡	12.5 (10.4, 14.9)*	23.2 (19.9, 27.0)*	1.63 (1.27, 2.08)*	2.30 (1.86, 2.83)*	2.35 (1.77, 3.11)*	2.19 (1.69, 2.84)*
	p-value	< 0.0001		0.018		0.36	

Adjusted for age, sex (male, female)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-9., continued

Visit 2 (1990-92)		Peripheral arterial disease		All-cause mortality	
		Black	White	Black	White
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	0.88 (0.50, 1.55)	1.50 (1.12, 2.01)*	0.97 (0.83, 1.13)	1.17 (1.08, 1.28)*
	≥7.0 mmol/L‡	2.64 (1.32, 5.25)*	3.69 (2.31, 5.89)*	1.17 (0.91, 1.51)	1.78 (1.50, 2.12)*
	p-value	0.28		0.0084	
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	1.05 (0.51, 2.17)	1.47 (0.99, 2.20)	1.10 (0.91, 1.33)	1.31 (1.16, 1.47)*
	≥7.0 mmol/L‡	2.83 (1.48, 5.42)*	3.22 (2.06, 5.04)*	1.21 (0.94, 1.55)	1.72 (1.46, 2.04)*
	p-value	0.72		0.026	

Adjusted for age, sex (male, female)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-9., continued

Visit 2 (1990-92)		Peripheral arterial disease		All-cause morality	
		Black	White	Black	White
ADA HbA1c definition	<39 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	39-46 mmol/mol	1.55 (0.86, 2.77)	1.86 (1.32, 2.63)*	1.20 (1.02, 1.40)*	1.63 (1.48, 1.80)*
	≥48 mmol/mol‡	3.62 (1.84, 7.10)*	6.24 (4.09, 9.51)*	1.62 (1.30, 2.03)*	1.89 (1.56, 2.29)*
	p-value	0.40		0.0027	
IEC HbA1c definition	<42 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	42-46 mmol/mol	1.86 (1.02, 3.41)*	1.87 (1.16, 3.02)*	1.18 (0.99, 1.40)	1.87 (1.64, 2.14)*
	≥48 mmol/mol‡	3.56 (1.87, 6.76)*	5.80 (3.83, 8.79)*	1.56 (1.26, 1.94)*	1.81 (1.49, 2.20)*
	p-value	0.41		0.0001	

Adjusted for age, sex (male, female)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-9., continued

Visit 4 (1996-98)		Incident diabetes		Chronic kidney disease		Atherosclerotic cardiovascular disease	
		Black	White	Black	White	Black	White
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	2.86 (2.30, 3.55)*	3.68 (3.28, 4.13)*	0.88 (0.68, 1.15)	1.14 (1.00, 1.29)*	1.10 (0.79, 1.53)	1.31 (1.10, 1.56)*
	≥7.0 mmol/L‡	16.4 (12.2, 22.0)*	29.5 (25.0, 34.8)*	1.24 (0.79, 1.96)	1.54 (1.19, 2.00)	1.11 (0.59, 2.08)	2.13 (1.56, 2.90)*
	p-value	0.017		0.21		0.16	
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	3.36 (2.64, 4.28)*	5.02 (4.37, 5.77)*	1.23 (0.86, 1.74)	1.24 (1.02, 1.50)*	1.00 (0.61, 1.62)	1.16 (0.88, 1.52)
	≥7.0 mmol/L‡	12.2 (9.29, 15.9)*	21.6 (18.5, 25.2)*	1.34 (0.86, 2.10)	1.51 (1.17, 1.95)*	1.07 (0.58, 1.98)	1.96 (1.44, 2.66)*
	p-value	0.0015		0.93		0.19	
ADA / WHO 2-hour glucose definition	<7.8 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	7.8-11.0 mmol/L	2.81 (2.24, 3.52)*	2.56 (2.26, 2.90)*	1.14 (0.86, 1.51)	1.18 (1.04, 1.35)*	0.90 (0.61, 1.33)	1.14 (0.95, 1.37)
	≥11.0 mmol/L‡	8.31 (6.51, 10.6)*	11.7 (10.3, 13.4)*	1.20 (0.83, 1.73)	1.46 (1.22, 1.74)*	1.13 (0.71, 1.82)	1.56 (1.24, 1.98)*
	p-value	0.018		0.67		0.32	

Adjusted for age, sex (male, female)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-9., continued

Visit 4 (1996-98)		Peripheral arterial disease		All-cause mortality	
		Black	White	Black	White
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	0.59 (0.23, 1.53)	1.25 (0.80, 1.96)	1.05 (0.81, 1.34)	1.18 (1.05, 1.34)*
	≥7.0 mmol/L‡	1.73 (0.50, 6.01)	2.09 (0.94, 4.61)	1.64 (1.09, 2.45)*	1.71 (1.35, 2.15)*
	p-value	0.36		0.75	
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	0.70 (0.16, 3.00)	0.59 (0.24, 1.46)	1.27 (0.90, 1.78)	1.31 (1.10, 1.57)*
	≥7.0 mmol/L‡	2.00 (0.59, 6.76)	1.84 (0.85, 3.98)	1.66 (1.12, 2.47)*	1.66 (1.32, 2.08)*
	p-value	0.98		0.99	
ADA / WHO 2-hour glucose definition	<7.8 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	7.8-11.0 mmol/L	0.69 (0.23, 2.07)	0.86 (0.53, 1.39)	1.23 (0.93, 1.62)	1.17 (1.03, 1.32)*
	≥11.0 mmol/L‡	1.42 (0.47, 4.26)	0.78 (0.37, 1.64)	1.65 (1.19, 2.28)	1.27 (1.07, 1.50)*
	p-value	0.59		0.46	

Adjusted for age, sex (male, female)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-10. Fully adjusted hazard ratios (95% CI) and p-values for interaction for incident outcomes by different clinical categories of prediabetes and undiagnosed diabetes, by race (visit 2: black N=2,299, white N=8,545; visit 4: black N=1,221, white N=5,973)

Visit 2 (1990-92)		Incident diabetes		Chronic kidney disease		Atherosclerotic cardiovascular disease	
		Black	White	Black	White	Black	White
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	2.05 (1.75, 2.40)*	2.30 (2.10, 2.53)*	1.00 (0.83, 1.19)	1.06 (0.96, 1.16)	1.01 (0.81, 1.27)	1.10 (0.97, 1.25)
	≥7.0 mmol/L‡	11.2 (9.03, 13.8)*	12.5 (10.7, 14.6)*	1.66 (1.26, 2.19)*	1.26 (1.02, 1.55)*	1.71 (1.23, 2.39)*	1.52 (1.19, 1.95)*
	p-value	0.16		0.17		0.69	
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	2.66 (2.26, 3.13)*	2.86 (2.57, 3.19)*	1.03 (0.82, 1.30)	1.13 (0.99, 1.30)	0.92 (0.70, 1.22)	1.07 (0.89, 1.27)
	≥7.0 mmol/L‡	9.25 (7.64, 11.2)*	9.70 (8.41, 11.2)*	1.68 (1.30, 2.18)*	1.25 (1.02, 1.54)*	1.67 (1.22, 2.28)*	1.46 (1.15, 1.85)*
	p-value	0.35		0.19		0.59	

Adjusted for age, sex (male, female), education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-10., continued

Visit 2 (1990-92)		Incident diabetes		Chronic kidney disease		Atherosclerotic cardiovascular disease	
		Black	White	Black	White	Black	White
ADA HbA1c definition	<39 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	39-46 mmol/mol	2.24 (1.92, 2.61)*	2.91 (2.63, 3.22)*	1.28 (1.07, 1.53)*	1.26 (1.11, 1.42)*	1.31 (1.05, 1.64)*	1.46 (1.27, 1.69)*
	≥48 mmol/mol‡	11.1 (9.10, 13.6)*	15.1 (12.8, 17.8)*	1.57 (1.20, 2.05)*	1.90 (1.52, 2.37)*	2.03 (1.49, 2.78)*	1.63 (1.24, 2.14)*
	p-value	<0.0001		0.29		0.35	
IEC HbA1c definition	<42 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	42-46 mmol/mol	2.60 (2.21, 3.05)*	3.64 (3.20, 4.14)*	1.20 (0.98, 1.46)	1.41 (1.19, 1.67)*	1.47 (1.15, 1.87)*	1.63 (1.35, 1.97)*
	≥48 mmol/mol‡	10.1 (8.31, 12.1)*	13.2 (11.3, 15.5)*	1.46 (1.12, 1.89)*	1.87 (1.50, 2.33)*	2.02 (1.50, 2.73)*	1.57 (1.20, 2.05)*
	p-value	<0.0001		0.069		0.40	

Adjusted for age, sex (male, female), education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-10., continued

Visit 2 (1990-92)		Peripheral arterial disease		All-cause mortality	
		Black	White	Black	White
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	0.88 (0.49, 1.58)	1.23 (0.91, 1.66)	0.92 (0.78, 1.07)	1.09 (1.00, 1.19)
	≥7.0 mmol/L‡	2.66 (1.25, 5.69)*	2.42 (1.46, 4.01)*	1.08 (0.82, 1.41)	1.53 (1.28, 1.83)*
	p-value	0.32		0.018	
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	1.06 (0.50, 2.23)	1.15 (0.77, 1.73)	1.03 (0.84, 1.25)	1.18 (1.05, 1.33)*
	≥7.0 mmol/L‡	2.91 (1.43, 5.90)*	2.21 (1.37, 3.56)*	1.14 (0.88, 1.48)	1.51 (1.27, 1.80)*
	p-value	0.77		0.045	

Adjusted for age, sex (male, female), education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-10., continued

Visit 2 (1990-92)		Peripheral arterial disease		All-cause morality	
		Black	White	Black	White
ADA HbA1c definition	<39 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	39-46 mmol/mol	1.45 (0.80, 2.64)	1.32 (0.93, 1.87)	1.14 (0.97, 1.33)	1.40 (1.27, 1.55)*
	≥48 mmol/mol‡	3.92 (1.87, 8.18)*	4.24 (2.67, 6.71)*	1.53 (1.21, 1.94)*	1.58 (1.29, 1.93)*
	p-value	0.59		0.022	
IEC HbA1c definition	<42 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	42-46 mmol/mol	1.80 (0.96, 3.36)	1.27 (0.78, 2.07)	1.09 (0.91, 1.31)	1.58 (1.38, 1.81)*
	≥48 mmol/mol‡	4.01 (1.98, 8.11)*	4.03 (2.56, 6.34)*	1.48 (1.18, 1.86)*	1.53 (1.25, 1.87)*
	p-value	0.57		0.0007	

Adjusted for age, sex (male, female), education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-10., continued

Visit 4 (1996-98)		Incident diabetes		Chronic kidney disease		Atherosclerotic cardiovascular disease	
		Black	White	Black	White	Black	White
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	2.65 (2.11, 3.32)*	2.87 (2.54, 3.23)*	0.86 (0.66, 1.14)	0.93 (0.81, 1.06)	0.97 (0.68, 1.37)	1.13 (0.95, 1.36)
	≥7.0 mmol/L‡	12.5 (8.99, 17.3)*	16.3 (13.6, 19.5)*	0.97 (0.60, 1.57)	1.14 (0.87, 1.50)	0.78 (0.40, 1.52)	1.66 (1.19, 2.30)*
	p-value	0.085		0.48		0.14	
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	3.16 (2.47, 4.06)*	3.67 (3.18, 4.23)*	1.30 (0.91, 1.87)	0.99 (0.81, 1.21)	0.94 (0.57, 1.54)	0.99 (0.75, 1.30)
	≥7.0 mmol/L‡	9.04 (6.69, 12.2)*	12.1 (10.3, 14.3)*	1.10 (0.68, 1.76)	1.18 (0.91, 1.54)	0.79 (0.41, 1.49)	1.56 (1.13, 2.14)*
	p-value	0.031		0.51		0.16	
ADA / WHO 2-hour glucose definition	<7.8 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	7.8-11.0 mmol/L	2.55 (2.01, 3.22)*	1.95 (1.71, 2.21)*	1.16 (0.86, 1.55)	1.06 (0.93, 1.21)	0.82 (0.54, 1.24)	1.01 (0.84, 1.22)
	≥11.0 mmol/L‡	7.27 (5.61, 9.41)*	7.80 (6.76, 9.01)*	1.11 (0.75, 1.62)	1.19 (0.99, 1.44)	0.89 (0.54, 1.47)	1.28 (1.00, 1.64)
	p-value	0.030		0.65		0.41	

Adjusted for age, sex (male, female), education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-10., continued

Visit 4 (1996-98)		Peripheral arterial disease		All-cause mortality	
		Black	White	Black	White
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	0.72 (0.27, 1.94)	0.96 (0.60, 1.54)	1.15 (0.88, 1.51)	1.12 (0.99, 1.27)
	≥7.0 mmol/L‡	2.22 (0.54, 9.09)	1.59 (0.69, 3.64)	1.68 (1.08, 2.60)*	1.67 (1.31, 2.14)*
	p-value	0.49		0.99	
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	1.16 (0.26, 5.26)	0.45 (0.18, 1.13)	1.41 (0.99, 2.00)	1.26 (1.05, 1.51)*
	≥7.0 mmol/L‡	2.59 (0.66, 10.2)	1.47 (0.66, 3.28)	1.67 (1.09, 2.54)*	1.65 (1.30, 2.09)*
	p-value	0.90		0.95	
ADA / WHO 2-hour glucose definition	<7.8 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	7.8-11.0 mmol/L	1.07 (0.33, 3.45)	0.81 (0.49, 1.33)	1.33 (0.99, 1.78)	1.16 (1.02, 1.32)*
	≥11.0 mmol/L‡	1.76 (0.52, 5.93)	0.66 (0.30, 1.42)	1.59 (1.13, 2.25)*	1.26 (1.06, 1.51)*
	p-value	0.66		0.56	

Adjusted for age, sex (male, female), education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-11. Demographic adjusted hazard ratios (95% CI) and p-values for interaction for incident outcomes by different clinical categories of prediabetes and undiagnosed diabetes, by sex (visit 2: male N=4,668, female N=6,176; visit 4: male N=3,015, female N=4,179)

Visit 2 (1990-92)		Incident diabetes		Chronic kidney disease		Atherosclerotic cardiovascular disease	
		Male	Female	Male	Female	Male	Female
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	2.59 (2.29, 2.93)*	3.14 (2.84, 3.48)*	1.13 (1.01, 1.27)*	1.22 (1.09, 1.37)*	1.16 (1.01, 1.34)*	1.34 (1.14, 1.58)*
	≥7.0 mmol/L‡	17.5 (14.6, 21.0)*	21.3 (18.3, 24.9)*	1.73 (1.38, 2.17)*	1.78 (1.43, 2.23)*	1.88 (1.46, 2.43)*	2.41 (1.84, 3.17)*
	p-value	0.064		0.81		0.27	
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	3.54 (3.12, 4.02)*	4.06 (3.58, 4.60)*	1.19 (1.02, 1.39)*	1.41 (1.19, 1.68)*	1.12 (0.92, 1.35)	1.42 (1.12, 1.79)*
	≥7.0 mmol/L‡	13.3 (11.3, 15.6)*	15.6 (13.5, 18.1)*	1.67 (1.34, 2.08)*	1.72 (1.38, 2.14)*	1.77 (1.38, 2.27)*	2.23 (1.71, 2.91)*
	p-value	0.13		0.49		0.19	

Adjusted for age, race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-11., continued

Visit 2 (1990-92)		Incident diabetes		Chronic kidney disease		Atherosclerotic cardiovascular disease	
		Male	Female	Male	Female	Male	Female
ADA HbA1c definition	<39 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	39-46 mmol/mol	3.43 (3.04, 3.88)*	3.40 (3.04, 3.80)*	1.37 (1.20, 1.58)*	1.47 (1.28, 1.68)*	1.56 (1.33, 1.83)*	1.92 (1.60, 2.29)*
	≥48 mmol/mol‡	21.1 (17.4, 25.7)*	20.6 (17.7, 24.0)*	2.05 (1.60, 2.61)*	2.06 (1.65, 2.56)*	1.98 (1.49, 2.63)*	2.92 (2.24, 3.80)*
	p-value	0.73		0.95		0.10	
IEC HbA1c definition	<42 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	42-46 mmol/mol	4.39 (3.77, 5.11)*	3.96 (3.46, 4.53)*	1.47 (1.22, 1.77)*	1.53 (1.28, 1.82)*	1.85 (1.52, 2.25)*	1.98 (1.59, 2.48)*
	≥48 mmol/mol‡	18.3 (15.1, 22.2)*	17.7 (15.2, 20.6)*	1.98 (1.56, 2.53)*	1.97 (1.58, 2.44)*	1.92 (1.45, 2.54)*	2.67 (2.06, 3.46)*
	p-value	0.77		0.95		0.27	

Adjusted for age, race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-11., continued

Visit 2 (1990-92)		Peripheral arterial disease		All-cause mortality	
		Male	Female	Male	Female
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	1.18 (0.85, 1.64)	1.56 (1.03, 2.36)*	1.03 (0.93, 1.13)	1.26 (1.13, 1.40)*
	≥7.0 mmol/L‡	1.82 (0.98, 3.37)	6.21 (3.69, 10.5)*	1.32 (1.08, 1.62)*	1.86 (1.52, 2.28)*
	p-value	0.0082		0.015	
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	1.23 (0.79, 1.89)	1.58 (0.88, 2.87)	1.09 (0.95, 1.24)	1.52 (1.31, 1.78)*
	≥7.0 mmol/L‡	1.73 (0.95, 3.14)	5.46 (3.34, 8.92)*	1.32 (1.08, 1.61)*	1.80 (1.48, 2.19)*
	p-value	0.0092		0.0028	

Adjusted for age, race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-11., continued

Visit 2 (1990-92)		Peripheral arterial disease		All-cause morality	
		Male	Female	Male	Female
ADA HbA1c definition	<39 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	39-46 mmol/mol	1.52 (1.03, 2.24)*	2.48 (1.56, 3.92)*	1.33 (1.19, 1.50)*	1.70 (1.50, 1.92)*
	≥48 mmol/mol‡	2.90 (1.61, 5.24)*	9.51 (5.83, 15.5)*	1.48 (1.19, 1.85)*	2.19 (1.81, 2.66)*
	p-value	0.0064		0.016	
IEC HbA1c definition	<42 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	42-46 mmol/mol	1.78 (1.10, 2.89)*	2.23 (1.25, 3.97)*	1.46 (1.26, 1.69)*	1.67 (1.43, 1.96)*
	≥48 mmol/mol‡	2.82 (1.57, 5.06)*	8.12 (5.06, 13.0)*	1.45 (1.16, 1.80)*	2.02 (1.67, 2.44)*
	p-value	0.017		0.14	

Adjusted for age, race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-11., continued

Visit 4 (1996-98)		Incident diabetes		Chronic kidney disease		Atherosclerotic cardiovascular disease	
		Male	Female	Male	Female	Male	Female
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	3.13 (2.67, 3.68)*	3.74 (3.28, 4.26)*	1.01 (0.86, 1.19)	1.15 (0.98, 1.36)*	1.21 (0.99, 1.48)	1.32 (1.04, 1.67)*
	≥7.0 mmol/L‡	28.2 (22.7, 35.2)*	23.5 (19.4, 28.5)*	1.39 (1.02, 1.89)*	1.51 (1.09, 2.10)*	1.75 (1.21, 2.52)*	1.88 (1.22, 2.90)*
	p-value	0.038		0.57		0.90	
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	3.76 (3.16, 4.48)*	5.42 (4.59, 6.40)*	1.03 (0.81, 1.31)	1.53 (1.20, 1.96)*	1.03 (0.76, 1.40)	1.25 (0.85, 1.84)
	≥7.0 mmol/L‡	20.1 (16.5, 24.6)*	17.6 (14.7, 21.2)*	1.39 (1.02, 1.88)*	1.51 (1.09, 2.09)*	1.62 (1.13, 2.32)*	1.76 (1.15, 2.70)*
	p-value	0.0042		0.089		0.80	
ADA / WHO 2-hour glucose definition	<7.8 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	7.8-11.0 mmol/L	2.32 (1.96, 2.75)*	2.75 (2.38, 3.17)*	1.11 (0.93, 1.33)	1.21 (1.03, 1.42)*	1.14 (0.91, 1.53)	1.03 (0.80, 1.31)
	≥11.0 mmol/L‡	11.0 (9.18, 13.1)*	10.4 (8.91, 12.2)*	1.20 (0.94, 1.54)	1.56 (1.26, 1.92)*	1.20 (0.88, 1.64)	1.71 (1.28, 2.28)*
	p-value	0.16		0.53		0.15	

Adjusted for age, race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-11., continued

Visit 4 (1996-98)		Peripheral arterial disease		All-cause mortality	
		Male	Female	Male	Female
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	1.42 (0.88, 2.29)	0.54 (0.22, 1.30)	1.05 (0.91, 1.21)	1.30 (1.10, 1.53)*
	≥7.0 mmol/L‡	1.92 (0.81, 4.58)	2.24 (0.78, 6.43)	1.38 (1.04, 1.82)*	2.18 (1.63, 2.90)*
	p-value	0.10		0.059	
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	0.72 (0.31, 1.67)	0.35 (0.05, 2.56)	1.29 (1.05, 1.57)*	1.32 (1.01, 1.71)*
	≥7.0 mmol/L‡	1.60 (0.69, 3.70)	2.45 (0.86, 6.94)	1.40 (1.06, 1.84)*	2.06 (1.55, 2.74)*
	p-value	0.63		0.24	
ADA / WHO 2-hour glucose definition	<7.8 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	7.8-11.0 mmol/L	0.89 (0.51, 1.56)	0.73 (0.36, 1.48)	1.28 (1.10, 1.49)*	1.07 (0.91, 1.26)
	≥11.0 mmol/L‡	1.09 (0.51, 2.31)	0.70 (0.24, 2.03)	1.14 (0.91, 1.43)	1.53 (1.25, 1.87)*
	p-value	0.82		0.018	

Adjusted for age, race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-12. Fully adjusted hazard ratios (95% CI) and p-values for interaction for incident outcomes by different clinical categories of prediabetes and undiagnosed diabetes, by sex (visit 2: male N=4,668, female N=6,176; visit 4: male N=3,015, female N=4,179)

Visit 2 (1990-92)		Incident diabetes		Chronic kidney disease		Atherosclerotic cardiovascular disease	
		Male	Female	Male	Female	Male	Female
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	2.22 (1.96, 2.51)*	2.35 (2.11, 2.61)*	1.05 (0.93, 1.18)	1.05 (0.93, 1.18)*	1.05 (0.91, 1.22)	1.13 (0.95, 1.34)
	≥7.0 mmol/L‡	12.5 (10.3, 15.1)*	12.8 (10.9, 15.1)*	1.49 (1.17, 1.88)*	1.36 (1.08, 1.72)*	1.56 (1.19, 2.03)*	1.64 (1.23, 2.19)*
	p-value	0.77		0.90		0.90	
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	2.91 (2.55, 3.31)*	2.85 (2.51, 3.24)*	1.06 (0.90, 1.24)	1.19 (1.00, 1.42)	0.98 (0.81, 1.18)	1.13 (0.88, 1.43)
	≥7.0 mmol/L‡	9.97 (8.39, 11.9)*	9.88 (8.46, 11.5)*	1.47 (1.16, 1.84)*	1.37 (1.09, 1.72)*	1.50 (1.16, 1.94)*	1.57 (1.19, 2.07)*
	p-value	0.57		0.55		0.77	

Adjusted for age, race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC), education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-12., continued

Visit 2 (1990-92)		Incident diabetes		Chronic kidney disease		Atherosclerotic cardiovascular disease	
		Male	Female	Male	Female	Male	Female
ADA HbA1c definition	<39 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	39-46 mmol/mol	2.95 (2.60, 3.35)*	2.52 (2.25, 2.83)*	1.29 (1.12, 1.48)*	1.26 (1.09, 1.45)*	1.33 (1.13, 1.56)*	1.53 (1.27, 1.85)*
	≥48 mmol/mol‡	15.6 (12.7, 19.1)*	12.6 (10.7, 14.7)*	1.89 (1.46, 2.43)*	1.58 (1.26, 1.99)*	1.56 (1.16, 2.09)*	2.03 (1.54, 2.68)*
	p-value	0.0082		0.66		0.59	
IEC HbA1c definition	<42 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	42-46 mmol/mol	3.78 (3.24, 4.41)*	2.76 (2.40, 3.16)*	1.32 (1.10, 1.59)*	1.29 (1.08, 1.55)*	1.54 (1.27, 1.88)*	1.53 (1.22, 1.93)*
	≥48 mmol/mol‡	13.4 (11.0, 16.4)*	11.0 (9.38, 12.8)*	1.82 (1.42, 2.34)*	1.53 (1.22, 1.92)*	1.54 (1.15, 2.06)*	1.89 (1.44, 2.48)*
	p-value	0.0003		0.67		0.70	

Adjusted for age, race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC), education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-12., continued

Visit 2 (1990-92)		Peripheral arterial disease		All-cause mortality	
		Male	Female	Male	Female
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	1.10 (0.78, 1.54)	1.26 (0.81, 1.95)	0.97 (0.88, 1.08)	1.14 (1.02, 1.28)*
	≥7.0 mmol/L‡	1.62 (0.84, 3.10)	3.71 (2.09, 6.59)*	1.17 (0.95, 1.45)	1.54 (1.24, 1.90)*
	p-value	0.057		0.043	
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	1.11 (0.71, 1.72)	1.16 (0.63, 2.13)	1.00 (0.88, 1.15)	1.32 (1.12, 1.54)*
	≥7.0 mmol/L‡	1.57 (0.84, 2.92)	3.35 (1.97, 5.70)	1.19 (0.97, 1.46)	1.52 (1.24, 1.86)*
	p-value	0.063		0.010	

Adjusted for age, race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC), education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-12., continued

Visit 2 (1990-92)		Peripheral arterial disease		All-cause morality	
		Male	Female	Male	Female
ADA HbA1c definition	<39 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	39-46 mmol/mol	1.23 (0.83, 1.82)	1.76 (1.09, 2.85)*	1.22 (1.08, 1.37)*	1.45 (1.28, 1.65)*
	≥48 mmol/mol‡	2.15 (1.16, 3.99)*	6.50 (3.74, 11.3)*	1.31 (1.04, 1.64)*	1.82 (1.48, 2.23)*
	p-value	0.016		0.037	
IEC HbA1c definition	<42 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	42-46 mmol/mol	1.43 (0.87, 2.33)	1.58 (0.87, 2.86)	1.30 (1.12, 1.51)*	1.41 (1.20, 1.66)*
	≥48 mmol/mol‡	2.16 (1.17, 3.97)*	5.68 (3.34, 9.64)*	1.28 (1.02, 1.61)*	1.69 (1.38, 2.06)*
	p-value	0.032		0.18	

Adjusted for age, race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC), education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-12., continued

Visit 4 (1996-98)		Incident diabetes		Chronic kidney disease		Atherosclerotic cardiovascular disease	
		Male	Female	Male	Female	Male	Female
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	2.65 (2.25, 3.12)*	2.92 (2.55, 3.35)*	0.87 (0.74, 1.03)	0.97 (0.82, 1.15)	1.06 (0.86, 1.31)	1.17 (0.91, 1.50)
	≥7.0 mmol/L‡	18.3 (14.4, 23.3)*	14.1 (11.5, 17.4)*	1.13 (0.81, 1.56)	1.10 (0.78, 1.55)	1.41 (0.96, 2.09)	1.41 (0.89, 2.21)
	p-value	0.085		0.57		0.94	
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	3.16 (2.65, 3.78)*	3.99 (3.36, 4.73)*	0.89 (0.69, 1.13)	1.29 (1.01, 1.66)*	0.91 (0.67, 1.24)	1.11 (0.75, 1.64)
	≥7.0 mmol/L‡	13.5 (10.8, 16.9)*	10.6 (8.70, 12.9)*	1.18 (0.86, 1.63)	1.16 (0.83, 1.62)	1.34 (0.92, 1.96)	1.33 (0.85, 2.08)
	p-value	0.035		0.068		0.86	
ADA / WHO 2-hour glucose definition	<7.8 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	7.8-11.0 mmol/L	1.93 (1.63, 2.30)*	2.14 (1.84, 2.48)*	1.04 (0.86, 1.25)	1.11 (0.94, 1.32)	1.03 (0.81, 1.29)	0.91 (0.71, 1.18)
	≥11.0 mmol/L‡	8.02 (6.60, 9.74)*	7.39 (6.28, 8.71)*	1.03 (0.80, 1.34)	1.33 (1.07, 1.67)*	0.99 (0.71, 1.37)	1.42 (1.05, 1.93)*
	p-value	0.28		0.40		0.15	

Adjusted for age, race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC), education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-12., continued

Visit 4 (1996-98)		Peripheral arterial disease		All-cause mortality	
		Male	Female	Male	Female
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	1.32 (0.80, 2.19)	0.47 (0.19, 1.16)	1.01 (0.87, 1.17)	1.27 (1.08, 1.51)*
	≥7.0 mmol/L‡	1.94 (0.78, 4.84)	1.71 (0.55, 5.30)	1.32 (0.98, 1.78)	2.20 (1.62, 2.98)*
	p-value	0.092		0.053	
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	0.67 (0.29, 1.58)	0.34 (0.05, 2.55)	1.24 (1.01, 1.53)*	1.32 (1.01, 1.72)
	≥7.0 mmol/L‡	1.57 (0.66, 3.76)	2.02 (0.67, 6.10)	1.38 (1.04, 1.84)*	2.07 (1.53, 2.79)*
	p-value	0.72		0.24	
ADA / WHO 2-hour glucose definition	<7.8 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	7.8-11.0 mmol/L	1.00 (0.56, 1.79)	0.65 (0.31, 1.36)	1.27 (1.09, 1.50)*	1.08 (0.91, 1.28)
	≥11.0 mmol/L‡	1.17 (0.53, 2.55)	0.58 (0.19, 1.75)	1.08 (0.85, 1.37)	1.57 (1.26, 1.95)*
	p-value	0.67		0.0071	

Adjusted for age, race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC), education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

ANCILLARY ANALYSES – Third National Health and Nutrition Examination Survey (NHANES III)

We conducted ancillary analyses in the Third National Health and Nutrition Examination Survey (NHANES III) for comparison to our results in the Atherosclerosis Risk in Communities (ARIC) Study. NHANES III (1988-1994) is a complex sample survey of the general non-institutionalized civilian population of the United States. Measurements of fasting glucose, hemoglobin A1c (HbA1c), and 2-hour glucose are available in NHANES III and can be linked with the National Death Index to provide prospective follow-up for mortality (1).

For these ancillary analyses, we limited our population to the 3,894 participants who were aged 40 or older, attended the morning fasting session of the NHANES III examination, who did not have diagnosed diabetes, and were not missing information on fasting glucose or HbA1c. For analyses of 2-hour glucose, our analyses were limited to the subsample of these persons (eligible participants aged 40-74 years) who had valid oral glucose tolerance tests (OGTT) (n=2,970). In prospective analyses, we excluded persons missing follow-up information (n=6 for all-cause mortality and n=23 for cardiovascular mortality). We conducted all analyses of NHANES III accounting for the complex survey design and weighted to represent the general U.S. non-institutionalized population of adults aged 40 or older.

We defined prediabetes using three definitions recognized by the American Diabetes Association (ADA): fasting glucose 5.6-6.9 mmol/L; HbA1c 39-46 mmol/mol; and 2-hour glucose 7.8-11.0 mmol/L, along with the additional definition recognized by the World Health Organization (WHO): fasting glucose 6.1-6.9 mmol/L; and

International Expert Committee (IEC): HbA1c 42-46 mmol/mol. We linked our sample with the National Death Index to obtain all-cause and cardiovascular mortality outcomes. Cardiovascular mortality was defined as deaths due to diseases of the heart (International Classification of Disease-10 Codes: I00-I09, I11, I13, I20-I51).

We compared baseline characteristics across the different clinical categories (normoglycemia, prediabetes, and undiagnosed diabetes). We calculated prevalence estimates for prediabetes overall and in the population of black and white persons aged 47-70 (to align with the ARIC Study visit 2 age range). We calculated sensitivity and specificity (and other relevant metrics) for each definition of prediabetes using 10-year Kaplan-Meier estimates comparing those with prediabetes to those with normoglycemia against those with and without the events of interest. Cox proportional hazards models were used to estimate adjusted hazard ratios of incident events associated with clinical categories, with normoglycemia as the reference group. Demographic adjusted models included age, sex, and race. Fully adjusted models included all variables in demographic adjusted models plus education level, body mass index, waist-to-hip ratio, total cholesterol, HDL-cholesterol, triglycerides, eGFR, hypertension, smoking status, alcohol use, and family history of diabetes. We used Harrell's C-statistic to compare discrimination of models with the different clinical categories with respect to future risk of all-cause and cardiovascular mortality. We provide here the results for all-cause and fatal coronary heart disease in ARIC for direct comparison to the results from NHANES III.

Characteristics of U.S. adults aged 40 or older without diagnosed diabetes are shown in **Table C-13**. Prediabetes prevalence estimates across definitions were similar,

although slightly lower as compared to ARIC (**Table C-14.A**). We observed similar patterns in prevalence to those observed in ARIC with ADA fasting glucose-defined prediabetes having the highest prevalence, followed by ADA/WHO 2-hour glucose. The ADA and IEC HbA1c- based definitions and WHO fasting glucose definition had the lowest prevalence. When NHANES III analyses were restricted to the same age and race groups as in the ARIC Study, prevalence estimates were more similar to ARIC (**Table C-14.B**).

During a median of approximately 18 years of follow-up, there were 1,860 total deaths and 467 cardiovascular deaths. Analyses of sensitivity and specificity comparing those with prediabetes by each definition to those with normoglycemia yielded similar results to ARIC. We found that WHO fasting glucose and the HbA1c-based definitions were more specific, but ADA fasting glucose and the ADA/WHO 2-hour glucose-based definitions were more sensitive (**Table C-15**).

With the exception of ADA/WHO 2-hour glucose defined prediabetes, all other definitions were significantly associated with all-cause mortality (**Table C-16**). Associations with cardiovascular mortality were less robust (**Table C-16**), likely due to limited precision as a result of the small number of events in this general population (**Table C-17**). Consistent with associations observed in the ARIC Study (**Table C-18**), hazard ratios for HbA1c-based definitions for all-cause mortality in NHANES III were higher than those for fasting glucose or 2-hour glucose-based definitions of prediabetes (**Table C-16**). For cardiovascular mortality in NHANES III, patterns were similar but HbA1c-based definitions were not consistently stronger, although it is difficult to draw firm conclusions due to the more limited power for this outcome. C-statistics were

generally similar across all definitions except 2-hour glucose, which were lower, however the limited number of events is, again, a concern.

References

1. National Center for Health Statistics. National Health and Nutrition Examination Survey NHANES III (1988-1994). 2015.

Table C-13. Baseline characteristics of U.S Adults aged 40+ without diagnosed diabetes by different definitions of prediabetes*, NHANES III (1988-1994)

N = 3,894	Normoglycemia	Prediabetes	Undiagnosed diabetes
	ADA Fasting glucose clinical categories		
	<5.6 mmol/L n = 2,252	5.6-6.9 mmol/L n = 1,402	≥7.0 mmol/L n = 240
Age (years)	55.4 (54.5-56.2)	59.1 (57.4-60.7)	61.8 (59.6-63.9)
Female, %	60.3 (57.2-63.4)	42.2 (38.3-46.0)	45.5 (35.4-55.5)
Black, %	8.71 (7.25-10.2)	8.64 (6.88-10.4)	11.1 (7.23-15.0)
Less than high school education, %	26.0 (23.1-28.9)	33.6 (29.4-37.8)	40.9 (31.3-50.5)
Body Mass Index (kg/m^2)	26.2 (25.9-26.5)	28.1 (27.7-28.6)	30.8 (29.8-31.9)
Obese (≥30 kg/m^2), %	19.1 (16.9-21.2)	31.2 (27.0-35.4)	56.8 (49.4-64.2)
Waist-to-hip ratio	0.91 (0.91-0.92)	0.96 (0.96-0.97)	1.00 (0.98-1.01)
Fasting glucose (mmol/L)	5.13 (5.10-5.15)	6.03 (6.00-6.06)	9.27 (8.84-9.70)
HbA1c (mmol/mol)	34.0 (33.7-34.3)	35.6 (35.3-35.9)	48.7 (45.4-51.9)
Hypercholesterolemia, %	77.4 (74.0-80.7)	83.0 (79.9-86.1)	95.4 (92.1-98.7)
Hypertension, %	27.7 (24.4-31.0)	38.4 (35.3-41.5)	58.0 (48.5-67.5)
Estimated glomerular filtration rate ($mL/min/1.73\ m^2$)	89.4 (88.0-90.8)	84.8 (82.4-87.1)	82.8 (78.9-86.8)
Current smoker, %	24.3 (21.7-26.9)	22.5 (19.0-26.0)	22.5 (15.8-29.3)
Current drinker, %	46.9 (42.6-51.3)	47.0 (42.7-51.4)	32.5 (22.1-42.9)
Family history of diabetes, %	41.6 (37.8-45.4)	41.9 (38.2-45.6)	49.8 (39.9-59.8)

Abbreviations: ADA, American Diabetes Association; HbA1c, hemoglobin A1c

Table C-13., continued

N = 3,894	Normoglycemia	Prediabetes	Undiagnosed diabetes
	WHO Fasting glucose clinical categories		
	<6.1 mmol/L n = 3,112	6.1-6.9 mmol/L n = 542	≥7.0 mmol/mol n = 240
Age (years)	56.0 (55.0-57.0)	61.0 (59.2-62.9)	61.8 (59.6-63.9)
Female, %	55.6 (53.3-57.9)	43.5 (38.2-48.8)	45.5 (35.4-55.5)
Black, %	8.63 (7.35-9.92)	9.08 (6.43-11.7)	11.1 (7.23-15.0)
Less than high school education, %	27.6 (24.6-30.5)	35.9 (29.2-42.5)	40.9 (31.3-50.5)
Body Mass Index (kg/m^2)	26.6 (26.3-26.9)	28.9 (28.1-29.6)	30.8 (29.8-31.9)
Obese (≥30 kg/m^2), %	21.5 (19.4-23.6)	35.4 (29.4-41.4)	56.8 (49.4-64.2)
Waist-to-hip ratio	0.92 (0.92-0.93)	0.98 (0.97-0.98)	1.00 (0.98-1.01)
Fasting glucose (mmol/L)	5.29 (5.27-5.32)	6.42 (6.38-6.46)	9.27 (8.84-9.70)
HbA1c (mmol/mol)	34.3 (34.1-34.5)	36.3 (35.8-36.8)	48.7 (45.4-51.9)
Hypercholesterolemia, %	78.7 (76.1-81.4)	83.1 (79.0-87.1)	95.4 (92.1-98.7)
Hypertension, %	29.7 (26.8-32.6)	43.1 (34.7-51.6)	58.0 (48.5-67.5)
Estimated glomerular filtration rate (mL/min/1.73 m^2)	88.5 (87.2-89.9)	82.7 (79.4-86.0)	82.8 (78.9-86.8)
Current smoker, %	24.4 (22.0-26.8)	18.1 (13.5-22.8)	22.5 (15.8-29.3)
Current drinker, %	47.4 (43.3-51.4)	44.1 (36.3-51.8)	32.5 (22.1-42.9)
Family history of diabetes, %	41.3 (38.2-44.4)	44.7 (38.5-51.0)	49.8 (39.9-59.8)

Abbreviations: WHO, World Health Organization; HbA1c, hemoglobin A1c

Table C-13., continued

N = 3,894	Normoglycemia	Prediabetes	Undiagnosed diabetes
	ADA HbA1c clinical categories		
	<39 mmol/mol n = 3,221	39-46 mmol/mol n = 574	≥48 mmol/mol n = 99
Age (years)	56.4 (55.4-57.3)	62.6 (60.8-64.3)	61.1 (57.6-64.6)
Female, %	54.2 (52.2-56.3)	51.4 (44.2-58.6)	49.1 (35.7-62.4)
Black, %	7.33 (6.20-8.46)	21.0 (17.5-24.5)	18.1 (9.80-26.3)
Less than high school education, %	27.6 (24.7-30.5)	44.0 (38.7-49.3)	46.0 (31.8-60.3)
Body Mass Index (kg/m^2)	26.8 (26.6-27.1)	28.5 (27.8-29.2)	31.6 (29.3-33.8)
Obese (≥30 kg/m^2), %	23.1 (20.9-25.3)	34.5 (27.9-41.1)	60.6 (46.1-75.1)
Waist-to-hip ratio	0.93 (0.92-0.94)	0.96 (0.95-0.98)	0.98 (0.95-1.01)
Fasting glucose (mmol/L)	5.43 (5.40-5.46)	6.22 (6.06-6.38)	11.8 (10.7-12.9)
2-hour glucose (mmol/L)	6.29 (6.16-6.42)	8.60 (8.01-9.18)	19.5 (18.0-21.0)
Hypercholesterolemia, %	78.8 (76.2-81.3)	89.3 (86.6-92.0)	94.9 (89.3-100.5)
Hypertension, %	30.8 (28.1-33.5)	46.5 (40.0-53.0)	59.1 (44.1-74.1)
Estimated glomerular filtration rate ($mL/min/1.73\ m^2$)	88.3 (87.0-89.5)	80.7 (77.2-84.3)	83.5 (74.8-92.2)
Current smoker, %	22.5 (20.3-24.6)	33.6 (27.1-40.0)	24.7 (13.4-36.1)
Current drinker, %	47.7 (43.8-51.6)	31.1 (25.0-37.2)	42.7 (25.4-60.0)
Family history of diabetes, %	41.8 (38.9-44.7)	43.1 (36.8-49.4)	46.2 (31.4-61.0)

Abbreviations: ADA, American Diabetes Association; HbA1c, hemoglobin A1c

Table C-13., continued

N = 3,894	Normoglycemia	Prediabetes	Undiagnosed diabetes
	IEC HbA1c clinical categories		
	<42 mmol/mol n = 3,646	42-46 mmol/L n = 149	≥48 mmol/L n = 99
Age (years)	56.8 (55.9-57.7)	65.2 (62.8-67.7)	61.1 (57.6-64.6)
Female, %	54.2 (52.2-56.1)	44.3 (34.8-53.8)	49.1 (35.7-62.4)
Black, %	8.36 (7.14-9.58)	24.6 (17.7-31.5)	18.1 (9.80-26.3)
Less than high school education, %	28.8 (26.0-31.7)	49.3 (39.1-59.5)	46.0 (31.8-60.3)
Body Mass Index (kg/m^2)	26.9 (26.7-27.2)	28.9 (27.7-30.1)	31.6 (29.3-33.8)
Obese (≥30 kg/m^2), %	23.9 (21.8-26.0)	40.5 (28.4-52.7)	60.6 (46.1-75.1)
Waist-to-hip ratio	0.93 (0.93-0.94)	0.98 (0.96-0.99)	0.98 (0.95-1.01)
Fasting glucose (mmol/L)	5.48 (5.44-5.51)	6.89 (6.56-7.21)	11.8 (10.7-12.9)
2-hour glucose (mmol/L)	6.41 (6.28-6.54)	11.2 (9.8-12.6)	19.5 (18.0-21.0)
Hypercholesterolemia, %	79.6 (77.3-81.9)	89.4 (83.8-95.0)	94.9 (89.3-100.5)
Hypertension, %	31.9 (29.5-34.4)	51.8 (39.2-64.4)	59.1 (44.1-74.1)
Estimated glomerular filtration rate ($mL/min/1.73\ m^2$)	87.7 (86.4-89.0)	78.6 (72.3-84.9)	83.5 (74.8-92.2)
Current smoker, %	23.5 (21.3-25.6)	29.6 (18.0-41.1)	24.7 (13.4-36.1)
Current drinker, %	46.4 (42.5-50.2)	29.2 (19.9-38.5)	42.7 (25.4-60.0)
Family history of diabetes, %	41.8 (39.0-44.6)	47.3 (35.0-59.5)	46.2 (31.4-61.0)

Abbreviations: IEC, International Expert Committee; HbA1c, hemoglobin A1c

Table C-13., continued

N = 2,970	Normoglycemia	Prediabetes	Undiagnosed diabetes
	ADA/WHO 2-hour glucose clinical categories		
	<7.8 mmol/L n = 2,137	7.8-11.0 mmol/L n = 578	≥11.0 mmol/L n = 255
Age (years)	52.9 (52.1-53.7)	57.1 (55.9-58.4)	60.5 (58.6-62.4)
Female, %	51.8 (49.2-54.5)	53.6 (47.9-59.3)	46.5 (36.7-56.3)
Black, %	8.91 (7.53-10.3)	8.11 (5.98-10.3)	8.53 (4.77-12.3)
Less than high school education, %	23.1 (19.7-26.6)	33.6 (28.6-38.7)	36.1 (25.6-46.6)
Body Mass Index (kg/m^2)	26.8 (26.4-27.1)	28.5 (27.7-29.2)	30.3 (29.2-31.5)
Obese (≥30 kg/m^2), %	21.6 (18.9-24.4)	35.8 (30.3-41.4)	56.9 (49.0-64.7)
Waist-to-hip ratio	0.92 (0.92-0.93)	0.96 (0.95-0.97)	0.99 (0.98-1.00)
Fasting glucose (mmol/L)	5.35 (5.32-5.38)	5.80 (5.71-5.90)	8.26 (7.73-8.79)
2-hour glucose (mmol/L)	34.2 (33.9-34.4)	35.6 (35.2-36.1)	45.4 (42.2-48.7)
Hypercholesterolemia, %	77.7 (74.8-80.6)	86.4 (82.2-90.6)	91.6 (86.9-96.3)
Hypertension, %	27.3 (23.9-30.7)	42.0 (35.9-48.1)	53.5 (43.7-63.4)
Estimated glomerular filtration rate ($mL/min/1.73\ m^2$)	91.6 (90.3-92.9)	87.6 (85.3-89.9)	83.2 (79.3-87.2)
Current smoker, %	27.2 (24.8-29.6)	17.6 (13.3-21.9)	23.5 (16.5-30.5)
Current drinker, %	51.5 (47.3-55.8)	39.3 (33.5-45.0)	44.6 (34.5-54.8)
Family history of diabetes, %	43.4 (39.9-46.9)	44.9 (37.7-52.0)	52.3 (42.6-62.0)

Abbreviations: ADA, American Diabetes Association; WHO, World Health Organization; HbA1c, hemoglobin A1c

Table C-14. Prevalence (95% confidence interval) of prediabetes by definition in U.S Adults aged 40+ without diagnosed diabetes overall and by race and age, NHANES III

(a) Overall (U.S. Adults 40+)

	N	Prevalence (95%CI)
ADA Fasting glucose, 5.6-6.9 mmol/L	3,894	32.2 (29.9-34.6)
WHO Fasting glucose, 6.1-6.9 mmol/L	3,894	11.6 (10.4-12.9)
ADA HbA1c, 39-46 mmol/mol	3,894	10.2 (9.0-11.5)
IEC HbA1c, 42-46 mmol/mol	3,894	2.3 (1.8-3.1)
ADA/WHO 2-hour glucose, 7.8-11.0 mmol/L	2,970	17.1 (15.1-19.2)

Abbreviations: ADA, American Diabetes Association; HbA1c, hemoglobin A1c; IEC, International Expert Committee; OGTT, oral glucose tolerance test; WHO, World Health Organization

(b) Black and white adults aged 47-70 (for consistency with ARIC Study design)

	N	Prevalence (95%CI)
ADA Fasting glucose, 5.6-6.9 mmol/L	1,476	32.6 (29.8-35.6)
WHO Fasting glucose, 6.1-6.9 mmol/L	1,476	12.0 (10.6-13.4)
ADA HbA1c, 39-46 mmol/mol	1,476	10.2 (8.5-12.1)
IEC HbA1c, 42-46 mmol/mol	1,476	2.5 (1.7-3.6)
ADA/WHO 2-hour glucose, 7.8-11.0 mmol/L	1,390	18.7 (16.4-21.2)

Abbreviations: ADA, American Diabetes Association; HbA1c, hemoglobin A1c; IEC, International Expert Committee; OGTT, oral glucose tolerance test; WHO, World Health Organization

Table C-15. 10-year sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio and corresponding 95% confidence intervals of incident clinical outcomes according to different definitions of prediabetes (vs. normoglycemia) at baseline

Outcome	ADA fasting glucose 5.6-6.9 mmol/L	WHO fasting glucose 6.1-6.9 mmol/L	ADA HbA1c 39-46 mmol/mol	IEC HbA1c 42-46 mmol/mol	ADA/WHO 2-hour glucose 7.8-11.0 mmol/L
All-cause mortality (n/N)	830/3,653	830/3,653	878/3,793	878/3,793	322/2,715
Sensitivity	0.45 (0.42, 0.49)	0.18 (0.16, 0.21)	0.20 (0.18, 0.23)	0.07 (0.05, 0.08)	0.25 (0.20, 0.30)
Specificity	0.64 (0.62, 0.66)	0.86 (0.85, 0.87)	0.86 (0.85, 0.88)	0.97 (0.96, 0.98)	0.79 (0.78, 0.81)
PPV	0.27 (0.25, 0.29)	0.28 (0.24, 0.32)	0.31 (0.27, 0.35)	0.39 (0.31, 0.48)	0.14 (0.11, 0.17)
NPV	0.80 (0.78, 0.82)	0.77 (0.77, 0.80)	0.78 (0.77, 0.80)	0.78 (0.76, 0.79)	0.89 (0.87, 0.90)
+LR	1.25 (1.14, 1.37)	1.33 (1.12, 1.57)	1.50 (1.27, 1.76)	2.14 (1.55, 2.95)	1.19 (0.97, 1.47)
-LR	0.86 (0.80, 0.92)	0.95 (0.92, 0.98)	0.92 (0.89, 0.96)	0.96 (0.95, 0.98)	0.95 (0.89, 1.01)
Cardiovascular mortality (n/N)	235/3,638	235/3,638	251/3,776	251/3,776	82/2,710
Sensitivity	0.45 (0.39, 0.52)	0.17 (0.13, 0.23)	0.18 (0.14, 0.24)	0.07 (0.04, 0.11)	0.27 (0.18, 0.38)
Specificity	0.62 (0.60, 0.64)	0.85 (0.84, 0.87)	0.85 (0.84, 0.86)	0.96 (0.96, 0.97)	0.79 (0.77, 0.80)
PPV	0.08 (0.06, 0.09)	0.08 (0.05, 0.10)	0.08 (0.06, 0.11)	0.12 (0.07, 0.18)	0.04 (0.02, 0.06)
NPV	0.94 (0.93, 0.95)	0.94 (0.93, 0.95)	0.94 (0.93, 0.94)	0.94 (0.93, 0.94)	0.97(0.96, 0.98)
+LR	1.19 (1.03, 1.38)	1.19 (0.89, 1.58)	1.24 (0.94, 1.62)	1.84 (1.13, 2.99)	1.27 (0.88, 1.83)
-LR	0.88 (0.79, 1.00)	0.97 (0.91, 1.03)	0.96 (0.90, 1.02)	0.97 (0.94, 1.00)	0.93 (0.81, 1.06)

Abbreviations: ADA, American Diabetes Association; IEC, International Expert Committee; HbA1c, hemoglobin A1c; PPV, positive predictive value; NPV, negative predictive value; WHO, World Health Organization; +LR, positive likelihood ratio, -LR, negative likelihood ratio

Table C-16. Adjusted hazard ratio and Harrell's C-statistic (95% confidence intervals) for incident outcomes by different clinical categories of prediabetes and undiagnosed diabetes

		All-cause mortality		Cardiovascular mortality	
		Demographic adjusted HR (95% CI)	**Fully adjusted HR (95% CI)**	**Demographic adjusted HR (95% CI)**	**Fully adjusted HR (95% CI)**
ADA fasting glucose definition	N	3,888	2,593	3,871	2,587
	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	1.17 (1.01, 1.36)*	1.17 (0.99, 1.39)	1.37 (1.03, 1.83)*	1.31 (0.91, 1.88)
	≥7.0 mmol/L‡	1.31 (0.97, 1.76)	1.30 (0.93, 1.82)	1.51 (1.01, 2.27)*	1.37 (0.82, 2.28)
	C-statistic (95% CI)	0.794 (0.784, 0.803)	0.805 (0.794, 0.816)	0.830 (0.813, 0.847)	0.847 (0.828, 0.866)
WHO fasting glucose definition	N	3,888	2,593	3,871	2,587
	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	1.20 (1.04, 1.39)*	1.13 (0.96, 1.33)	1.06 (0.78, 1.46)	0.98 (0.68, 1.42)
	≥7.0 mmol/L‡	1.26 (0.95, 1.67)	1.23 (0.91, 1.68)	1.32 (0.91, 1.90)	1.17 (0.75, 1.83)
	C-statistic (95% CI)	0.794 (0.784, 0.803)	0.804 (0.793, 0.816)	0.830 (0.813, 0.847)	0.847 (0.828, 0.865)
ADA HbA1c definition	N	3,888	2,593	3,871	2,587
	<39 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	39-46 mmol/mol	1.42 (1.21, 1.66)*	1.17 (1.02, 1.35)*	1.27 (0.86, 1.88)	0.92 (0.59, 1.44)
	≥48 mmol/mol‡	1.06 (0.64, 1.75)	1.30 (0.76, 2.21)	0.68 (0.23, 2.04)	0.64 (0.29, 1.41)
	C-statistic (95% CI)	0.794 (0.784, 0.803)	0.804 (0.793, 0.816)	0.830 (0.813, 0.847)	0.847 (0.828, 0.866)

Demographic adjusted included age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC); Fully adjusted included demographic adjusted + education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), family history of diabetes (yes, no)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-16., continued

		All-cause mortality		Cardiovascular mortality	
		Demographic adjusted HR (95% CI)	**Fully adjusted HR (95% CI)**	**Demographic adjusted HR (95% CI)**	**Fully adjusted HR (95% CI)**
IEC HbA1c definition	N	3,888	2,593	3,871	2,587
	<42 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	42-46 mmol/mol	1.49 (1.20, 1.84)*	1.34 (1.06, 1.70)*	1.63 (1.00, 2.64)*	1.53 (0.92, 2.55)
	≥48 mmol/mol‡	1.02 (0.61, 1.70)	1.28 (0.75, 2.17)	0.67 (0.22, 2.02)	0.68 (0.31, 1.51)
	C-statistic (95% CI)	0.794 (0.784, 0.803)	0.804 (0.793, 0.816)	0.831 (0.814, 0.848)	0.847 (0.829, 0.866)
ADA / WHO 2-hour glucose definition	N	2,968	1,981	2,961	1,978
	<7.8 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	7.8-11.0 mmol/L	1.02 (0.85, 1.22)	1.10 (0.90, 1.35)	1.13 (0.78, 1.64)	1.10 (0.69, 1.76)
	≥11.0 mmol/L‡	1.46 (1.10, 1.92)*	1.43 (0.99, 2.05)	1.17 (0.70, 1.97)	0.96 (0.54, 1.71)
	C-statistic (95% CI)	0.749 (0.735, 0.763)	0.770 (0.754, 0.787)	0.796 (0.770, 0.822)	0.829 (0.800, 0.858)

Demographic adjusted included age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC); Fully adjusted included demographic adjusted + education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), family history of diabetes (yes, no)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-17. Number of all-cause and cardiovascular mortality events by different clinical categories of prediabetes and undiagnosed diabetes

	ADA Fasting glucose			WHO Fasting glucose			ADA HbA1c		
	<5.6 mmol/L	**5.6-6.9 mmol/L**	**≥7.0 mmol/L**	**<6.1 mmol/L**	**6.1-6.9 mmol/L**	**≥7.0 mmol/L**	**<39 mmol/ mol**	**39-46 mmol/ mol**	**≥48 mmol/ mol**
All-cause mortality (n/N)	962/ 2,248	748/ 1,401	150/239	1,402/ 3,108	308/ 541	150/239	1,465/ 3,217	343/ 572	52/99
Cardiovascular Mortality (n/N)	229/ 2,240	199/ 1,395	39/236	353/ 3,094	75/ 541	39/236	374/ 3,205	83/ 568	10/98
	IEC HbA1c			**ADA/WHO 2-hour glucose**					
	<42 mmol/ mol	**42-46 mmol/mol**	**≥48 mmol/ mol**	**<7.8 mmol/L**	**7.8-11.0 mmol/L**	**≥11.0 mmol/L**			
All-cause mortality (n/N)	1,706/ 3,641	102/ 148	52/99	690/ 2,137	244/ 578	145/253			
Cardiovascular Mortality (n/N)	428/ 3,626	29/ 147	10/98	155/ 2,132	55/ 578	29/251			

Abbreviations: ADA, American Diabetes Association; HbA1c, hemoglobin A1c; IEC, International Expert Committee; WHO, World Health Organization

Table C-18. Adjusted hazard ratio and Harrell's C-statistic (95% confidence intervals) for incident outcomes in ARIC by different clinical categories of prediabetes and undiagnosed diabetes

Visit 2 (1990-92)		All-cause mortality		Fatal Coronary Heart disease	
		Demographic adjusted HR (95% CI)	Fully adjusted HR (95% CI)	Demographic adjusted HR (95% CI)	Fully adjusted HR (95% CI)
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	1.12 (1.04, 1.21)*	1.05 (0.97, 1.13)	1.23 (0.95, 1.60)	1.02 (0.78, 1.33)
	≥7.0 mmol/L‡	1.55 (1.35, 1.79)*	1.35 (1.16, 1.57)*	2.95 (2.01, 4.34)*	2.08 (1.38, 3.14)*
	C-statistic (95% CI)	0.683 (0.674, 0.692)	0.720 (0.711, 0.729)	0.730 (0.700, 0.760)	0.792 (0.766, 0.819)
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	1.25 (1.13, 1.38)*	1.12 (1.01, 1.24)*	1.37 (0.98, 1.91)	1.10 (0.78, 1.55)
	≥7.0 mmol/L‡	1.52 (1.32, 1.75)*	1.35 (1.17, 1.56)*	2.81 (1.94, 4.05)*	2.10 (1.42, 3.10)*
	C-statistic (95% CI)	0.683 (0.674, 0.693)	0.720 (0.711, 0.729)	0.731 (0.701, 0.761)	0.792 (0.766, 0.819)
ADA HbA1c definition	<39 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	39-46 mmol/mol	1.49 (1.37, 1.62)*	1.31 (1.21, 1.43)*	2.31 (1.76, 3.02)*	1.77 (1.34, 2.33)*
	≥48 mmol/mol‡	1.81 (1.57, 2.10)*	1.56 (1.34, 1.82)*	2.89 (1.87, 4.45)*	1.97 (1.25, 3.10)*
	C-statistic (95% CI)	0.688 (0.679, 0.697)	0.722 (0.713, 0.731)	0.746 (0.717, 0.774)	0.797 (0.771, 0.823)
IEC HbA1c definition	<42 mmol/mol	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	42-46 mmol/mol	1.56 (1.40, 1.73)*	1.35 (1.21, 1.51)*	2.49 (1.81, 3.42)*	1.83 (1.33, 2.53)*
	≥48 mmol/mol‡	1.73 (1.50, 1.99)*	1.50 (1.30, 1.75)*	2.58 (1.68, 3.95)*	1.80 (1.16, 2.81)*
	C-statistic (95% CI)	0.687 (0.678, 0.696)	0.722 (0.713, 0.730)	0.738 (0.708, 0.767)	0.794 (0.767, 0.820)

Demographic adjusted included age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

Fully adjusted included demographic adjusted + education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Table C-18., continued

Visit 4 (1996-98)		All-cause mortality		Fatal Coronary Heart disease	
		Demographic adjusted HR (95% CI)	Fully adjusted HR (95% CI)	Demographic adjusted HR (95% CI)	Fully adjusted HR (95% CI)
ADA fasting glucose definition	<5.6 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	5.6-6.9 mmol/L	1.15 (1.03, 1.28)*	1.13 (1.01, 1.26)*	1.44 (0.97, 2.13)	1.21 (0.81, 1.83)
	≥7.0 mmol/L‡	1.68 (1.37, 2.05)*	1.68 (1.36, 2.08)*	2.92 (1.59, 5.35)*	2.25 (1.18, 4.30)*
	C-statistic (95% CI)	0.686 (0.673, 0.699)	0.714 (0.702, 0.727)	0.748 (0.703, 0.793)	0.786 (0.745, 0.827)
WHO fasting glucose definition	<6.1 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	6.1-6.9 mmol/L	1.29 (1.10, 1.51)*	1.29 (1.09, 1.51)*	1.76 (1.05, 2.93)*	1.53 (0.91, 2.59)
	≥7.0 mmol/L‡	1.65 (1.35, 2.01)*	1.66 (1.35, 2.04)*	2.73 (1.52, 4.91)*	2.22 (1.19, 4.13)*
	C-statistic (95% CI)	0.687 (0.673, 0.700)	0.715 (0.702, 0.727)	0.748 (0.703, 0.793)	0.787 (0.746, 0.827)
ADA / WHO 2-hour glucose definition	<7.8 mmol/L	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
	7.8-11.0 mmol/L	1.17 (1.05, 1.31)*	1.18 (1.05, 1.33)*	1.25 (0.82, 1.91)	1.13 (0.73, 1.75)
	≥11.0 mmol/L‡	1.33 (1.15, 1.55)*	1.33 (1.14, 1.56)*	1.78 (1.07, 2.96)*	1.43 (0.83, 2.46)
	C-statistic (95% CI)	0.685 (0.672, 0.698)	0.714 (0.701, 0.726)	0.745 (0.701, 0.789)	0.783 (0.743, 0.824)

Demographic adjusted included age, sex (male, female), race-center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC)

Fully adjusted included demographic adjusted + education level (less than high school, high school or equivalent, college or above), BMI, waist-to-hip ratio, total cholesterol, HDL, triglycerides, hypertension (yes, no), eGFR, smoking status (current, former, never), drinking status (current, former, never), lipid-lowering medication use (yes, no), family history of diabetes (yes, no)

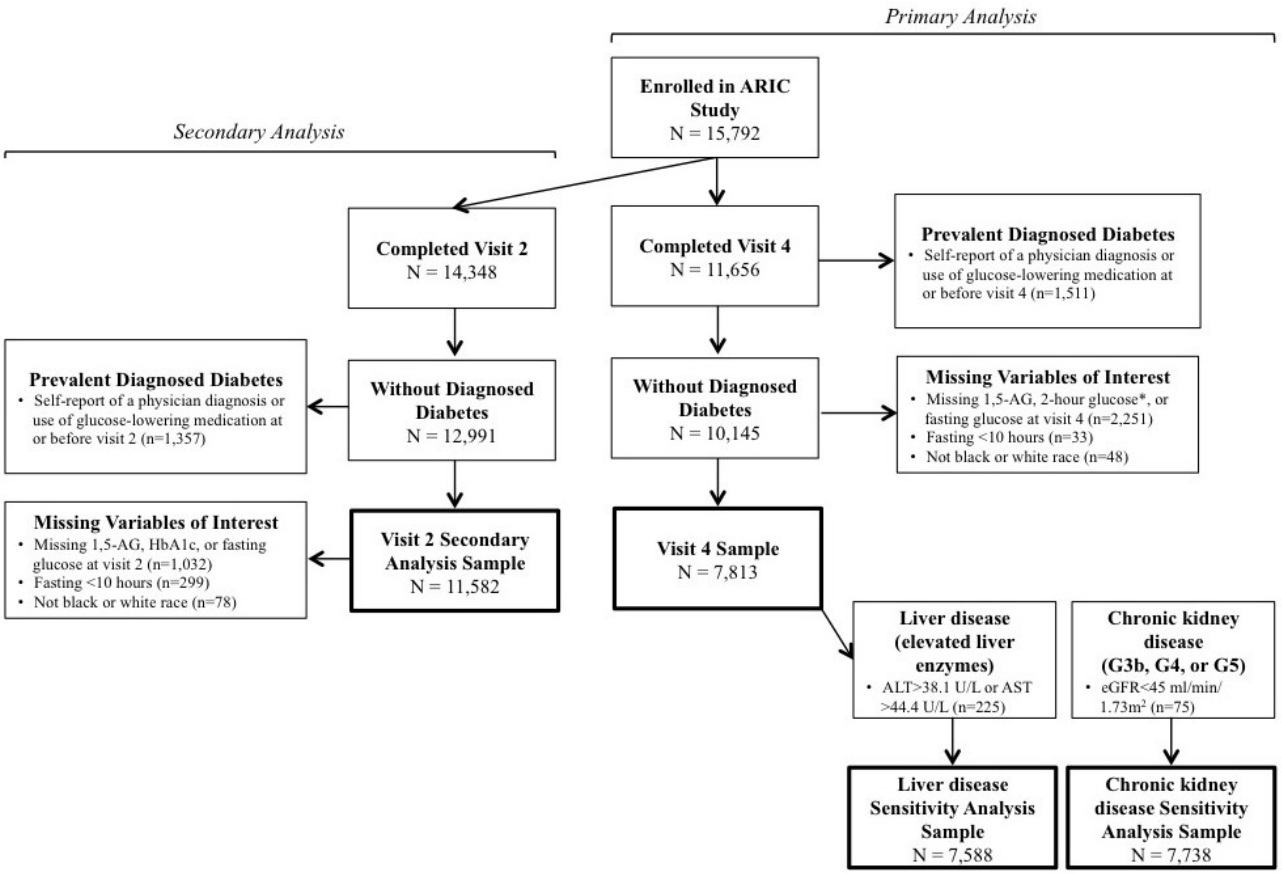
‡ Undiagnosed diabetes

* $p < 0.05$

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; HbA1c, hemoglobin A1c; HR, hazard ratio; IEC, International Expert Committee; WHO, World Health Organization

Appendix D: Supplementary Materials for Chapter 3

Figure D-1. 7,813 ARIC study participants without diagnosed diabetes included in this analysis



* Eligibility for oral glucose tolerance test (2-hour glucose measurement): those without prevalent diabetes, not on kidney dialysis, who had not had surgery to remove part of stomach or small intestine, who fasted for least 10 hours, and who were willing to participate; also excluded those who did not finish all of the solution (residual amount ≥145ml), were missing timing information timing of the test or whose post-challenge blood draw did not fall within 110-130 minutes after glucola

Table D-1. Categories of hyperglycemia based on clinical cut-points for diabetes

	Category	ARIC study visit (dates)
Primary analyses	2-hour glucose ≥200 mg/dL Fasting glucose ≥126 mg/dL 2-hour glucose ≥200 mg/dL and fasting glucose ≥126 mg/dL	Visit 4 (1996-98)
Secondary analyses	HbA1c ≥6.5% HbA1c ≥6.5% and fasting glucose ≥126 mg/dL	Visit 2 (1990-92)

Figure D-2. Scatterplots of 1,5-AG with lowess curves and Spearman's (*p*) and Pearson's (*r*) correlations of 2-hour glucose and fasting glucose among ARIC participants without diagnosed diabetes, n=7,813

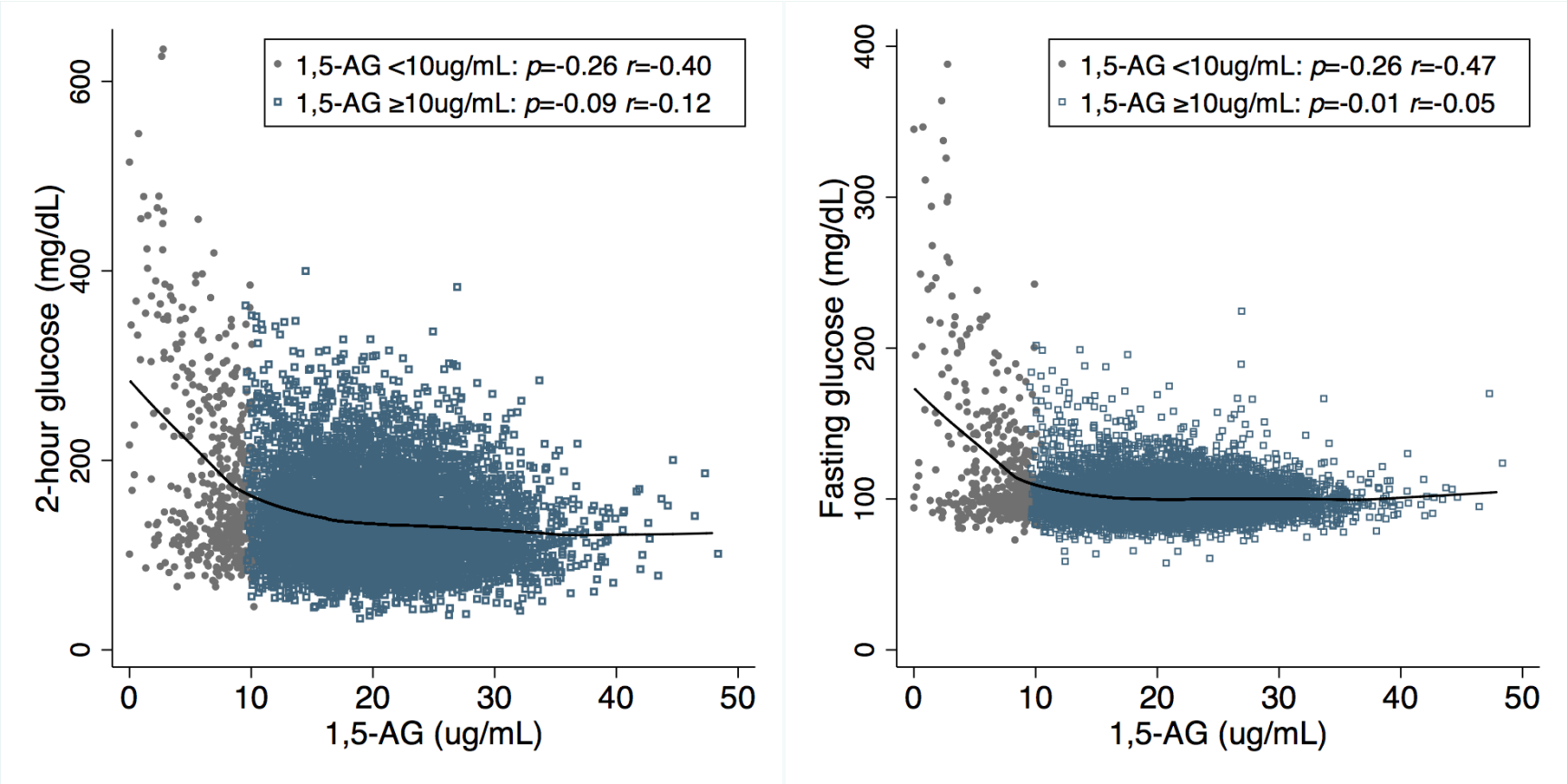


Table D-2. Performance of 1,5-AG <10 µg/mL compared to identify elevated 2-hour glucose and/or fasting glucose excluding those with G3b, G4, and G5 chronic kidney disease, n=7,738

1,5-AG cut point	Sensitivity	Specificity	+Likelihood Ratio	-Likelihood Ratio	Positive predictive value	Negative predictive value
1,5-AG compared to 2-hour glucose ≥ 200 mg/dL (n=807)						
Area under the ROC: 0.66 (0.64, 0.68)						
< 10 µg/mL	19.3%	96.1%	4.98	0.84	36.7%	91.1%
(n = 425)	(16.7, 22.2)	(95.6, 96.6)	(4.15, 5.98)	(0.81, 0.87)	(32.1, 41.5)	(90.4, 91.7)
1,5-AG compared to fasting glucose ≥ 126 mg/dL (n=394)						
Area under the ROC: 0.72 (0.69, 0.75)						
< 10 µg/mL	31.2%	95.9%	7.59	0.72	28.9%	96.3%
(n = 425)	(26.7, 36.0)	(95.4, 96.3)	(6.32, 9.12)	(0.67, 0.77)	(24.7, 33.5)	(95.8, 96.7)
1,5-AG compared to 2-hour glucose ≥ 200 mg/dL and fasting glucose ≥ 126 mg/dL (n=311)						
Area under the ROC: 0.78 (0.745, 0.81)						
< 10 µg/mL	38.3%	95.9%	9.29	0.64	28.0%	97.4%
(n = 425)	(32.8, 43.9)	(95.4, 96.3)	(7.77, 11.1)	(0.59, 0.70)	(23.8, 32.5)	(97.0, 97.7)

Table D-3. Performance of 1,5-AG <10 µg/mL compared to identify elevated 2-hour glucose and/or fasting glucose excluding those with elevated liver enzymes (ALT >38.1 U/L or AST > 44.4 U/L), n=7,588

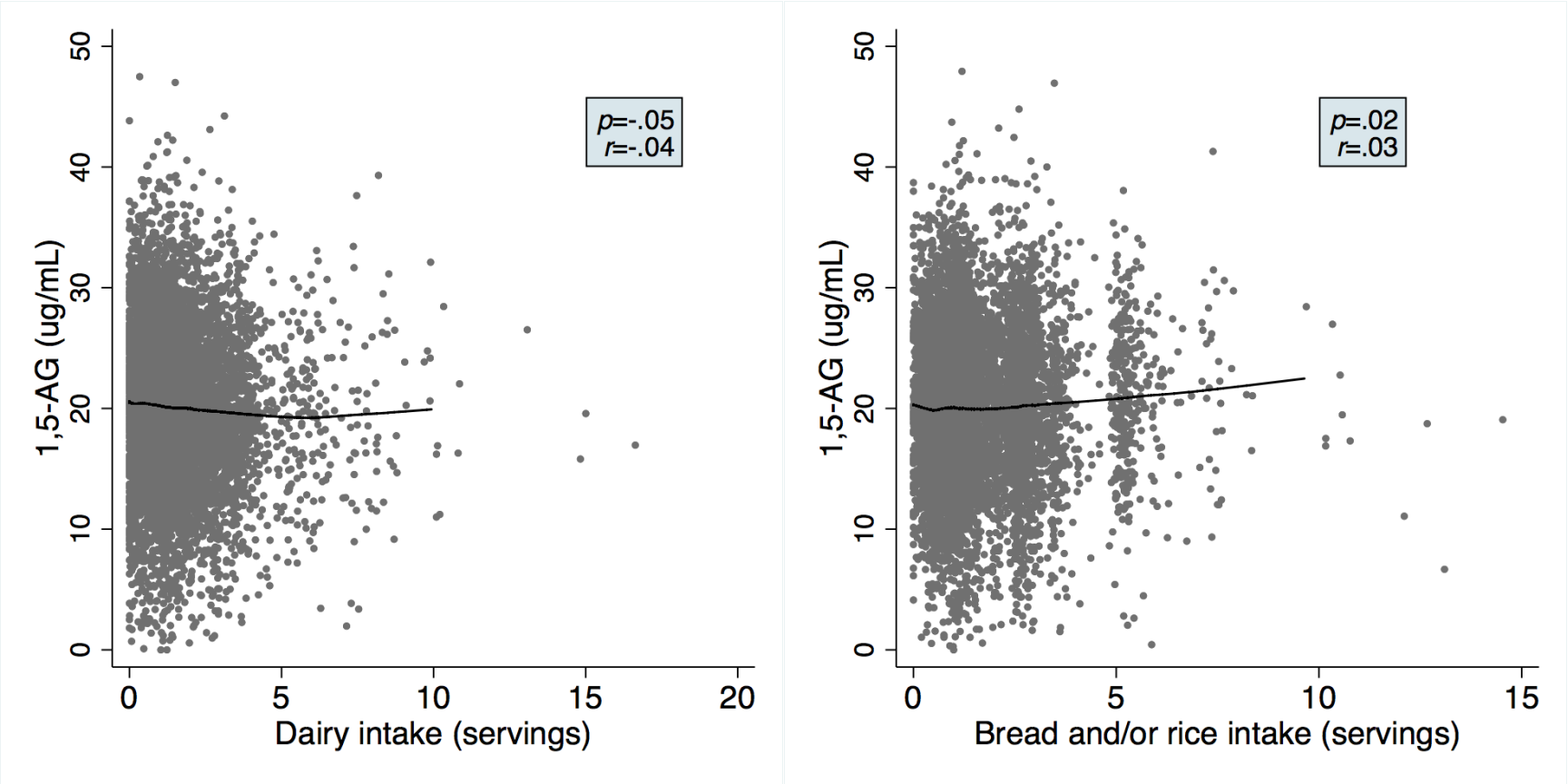
1,5-AG cut point	Sensitivity	Specificity	+Likelihood Ratio	-Likelihood Ratio	Positive predictive value	Negative predictive value
1,5-AG compared to 2-hour glucose ≥ 200 mg/dL (n=775)						
Area under the ROC: 0.66 (0.64, 0.68)						
< 10 µg/mL	18.6%	96.1%	4.71	0.85	34.9%	91.2%
(n = 413)	(15.9, 21.5)	(95.6, 96.5)	(3.90, 5.68)	(0.82, 0.88)	(30.3, 39.7)	(90.5, 91.9)
1,5-AG compared to fasting glucose ≥ 126 mg/dL (n=372)						
Area under the ROC: 0.72 (0.69, 0.75)						
< 10 µg/mL	30.4%	95.8%	7.31	0.73	27.4%	96.4%
(n = 413)	(25.7, 35.3)	(95.4, 96.3)	(6.04, 8.83)	(0.68, 0.78)	(23.1, 31.9)	(95.9, 96.8)
1,5-AG compared to 2-hour glucose ≥ 200 mg/dL and fasting glucose ≥ 126 mg/dL (n=293)						
Area under the ROC: 0.78 (0.74, 0.81)						
< 10 µg/mL	37.2%	95.8%	8.93	0.66	26.4%	97.4%
(n = 413)	(31.7, 43.0)	(95.3, 96.3)	(7.42, 10.7)	(0.60, 0.72)	(22.2, 30.9)	(97.0, 97.8)

Abbreviations: 1,5-AG, 1,5-anhydroglucitol; ALT, alanine aminotransferase; AST, aspartate aminotransferase

Table D-4. Performance of 1,5-AG <10 µg/mL compared to identify elevated HbA1c and/or elevated fasting glucose, measured from ARIC Visit 2 samples (1990-92), n=11,582

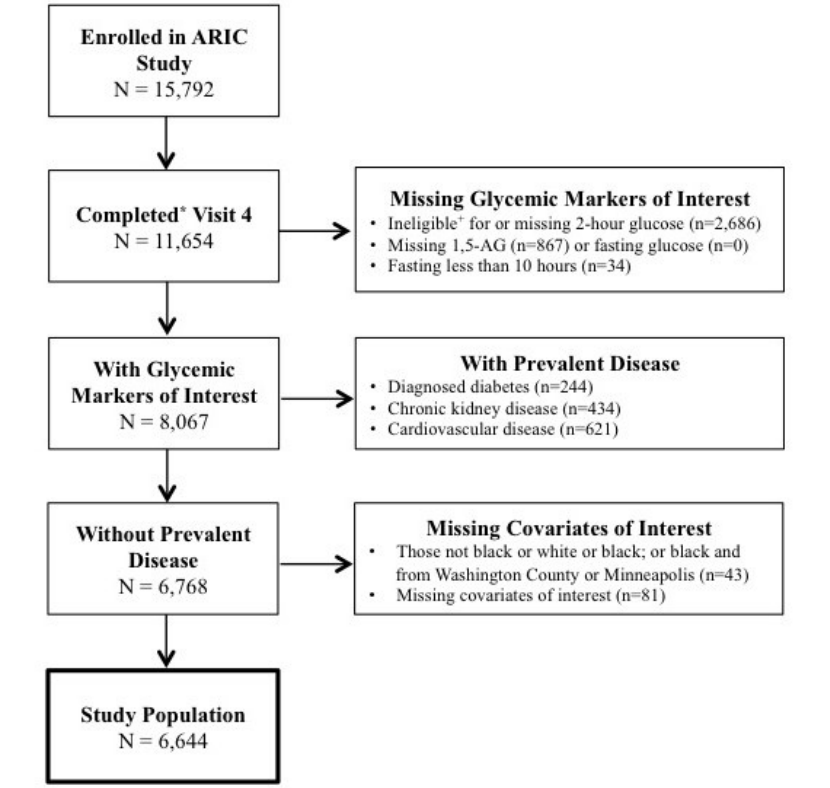
1,5-AG cut point	Sensitivity	Specificity	+Likelihood Ratio	-Likelihood Ratio	Positive predictive value	Negative predictive value
1,5-AG compared to HbA1c ≥ 6.5% (n=470)						
Area under the ROC: 0.74 (0.71, 0.77)						
< 10 µg/mL	27.3%	95.0%	5.41	0.77	27.6%	94.9%
(n = 754)	(24.2, 30.6)	(94.5, 95.4)	(4.69, 6.23)	(0.73, 0.80)	(24.4, 30.9)	(94.5, 95.3)
1,5-AG compared to fasting glucose ≥ 126 mg/dL (n=762)						
Area under the ROC: 0.67 (0.64, 0.69)						
< 10 µg/mL	37.9%	94.8%	7.31	0.66	23.6%	97.3%
(n = 754)	(33.5, 42.4)	(94.4, 95.2)	(6.35, 8.41)	(0.61, 0.70)	(20.6, 26.8)	(97.0, 97.6)
1,5-AG compared to HbA1c ≥ 6.5% and fasting glucose ≥ 126 mg/dL (n=344)						
Area under the ROC: 0.80 (0.77, 0.83)						
< 10 µg/mL	47.7%	94.7%	9.08	0.55	21.8%	98.3%
(n = 754)	(42.3, 53.1)	(94.3, 95.2)	(7.93, 10.4)	(0.50, 0.61)	(18.9, 24.9)	(98.1, 98.6)

Figure D-3. Scatterplots of 1,5-AG with lowess curves and Spearman's (*p*) and Pearson's (*r*) correlations of dairy intake and bread and/or rice intake among ARIC participants without diagnosed diabetes, n=7,813



Appendix E: Supplementary Materials for Chapter 4

Figure E-1. ARIC participants who attended Visit 4 (1996-98) without prevalent diabetes, chronic kidney disease, or cardiovascular disease included in our analysis, n=6,644



* Completed defined as those who attended visit and have follow-up time after the visit
+ Eligibility for oral glucose tolerance test (2-hour glucose measurement): those without prevalent diabetes, not on kidney dialysis, who had not had surgery to remove part of stomach or small intestine, who fasted for least 10 hours, and who were willing to participate; also excluded those missing timing information on the oral glucose tolerance test or whose post-challenge blood draw did not fall within 110-130 minutes after glucola

Table E-1. Adjusted hazard ratios and 95% CI of categories of 1,5-AG, 2-hour glucose, and fasting glucose for risk of incident diagnosed diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality, n=6,644

Biomarker Categories	Diagnosed diabetes		Chronic kidney disease	
	Model 1	**Model 2**	**Model 1**	**Model 2**
1,5-AG ≥10 µg/mL	1 (REF)	1 (REF)	1 (REF)	1 (REF)
1,5-AG <10 µg/mL	**2.71** (2.31, 3.16)	**2.74** (2.34, 3.20)	1.11 (0.89, 1.39)	1.05 (0.84, 1.31)
2-hour glucose <200 mg/dL	1 (REF)	1 (REF)	1 (REF)	1 (REF)
2-hour glucose ≥200 mg/dL	**6.98** (6.25, 7.78)	**5.30** (4.73, 5.94)	**1.31** (1.11, 1.54)	1.06 (0.90, 1.35)
Fasting glucose <126 mg/dL	1 (REF)	1 (REF)	1 (REF)	1 (REF)
Fasting glucose ≥126 mg/dL	**13.2** (11.5, 15.0)	**8.14** (7.07, 9.38)	**1.40** (1.12, 1.74)	1.04 (0.83, 1.31)
	Cardiovascular disease		**All-cause mortality**	
	Model 1	**Model 2**	**Model 1**	**Model 2**
1,5-AG ≥10 µg/mL	1 (REF)	1 (REF)	1 (REF)	1 (REF)
1,5-AG <10 µg/mL	1.18 (0.89, 1.57)	1.15 (0.87, 1.53)	1.02 (0.84, 1.25)	1.01 (0.82, 1.23)
2-hour glucose <200 mg/dL	1 (REF)	1 (REF)	1 (REF)	1 (REF)
2-hour glucose ≥200 mg/dL	**1.46** (1.20, 1.78)	1.21 (0.99, 1.49)	**1.27** (1.11, 1.45)	**1.23** (1.07, 1.42)
Fasting glucose <126 mg/dL	1 (REF)	1 (REF)	1 (REF)	1 (REF)
Fasting glucose ≥126 mg/dL	**1.67** (1.29, 2.16)	1.28 (0.98, 1.67)	**1.56** (1.30, 1.87)	**1.49** (1.24, 1.80)

Bold indicates $p<0.05$

Model 1: age, sex, race-center

Model 2: Model 1 + body mass index, systolic blood pressure, hypertension medication use (no, yes), total cholesterol, HDL, triglycerides, education (less than high school, high school/vocational school, college or higher), smoking status (current, former, never), drinking status (current, former, never), history of parental diabetes (no, yes), $eGFR_{cr}$, and log albumin-to-creatinine ratio

Table E-2. Differences in Harrell's C-statistics from adjusted associations of 1,5-AG, 2-hour glucose, and fasting glucose with incident diagnosed diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality modeled with restricted cubic splines, n=6,644

	Differences in Harrell's C-statistic (95% CI)			
	Diagnosed diabetes		**Chronic kidney disease**	
	Model 1	Model 2	Model 1	Model 2
2-hour glucose – 1,5-AG	**0.14** (0.13, 0.16)	**0.06** (0.05, 0.07)	**0.01** (0.00, 0.01)	0.00 (0.00, 0.00)
Fasting glucose – 1,5-AG	**0.15** (0.13, 0.17)	**0.06** (0.05, 0.07)	**0.00** (0.00, 0.01)	0.00 (0.00, 0.00)
	Cardiovascular disease		**All-cause mortality**	
	Model 1	Model 2	Model 1	Model 2
2-hour glucose – 1,5-AG	**0.01** (0.00, 0.01)	0.00 (0.00, 0.00)	**0.00** (0.00, 0.01)	0.00 (0.00, 0.00)
Fasting glucose – 1,5-AG	0.01 (0.00, 0.01)	0.00 (0.00, 0.01)	**0.00** (0.00, 0.01)	0.00 (0.00, 0.00)

Bold indicates $p<0.05$

Model 1: age, sex, race-center

Model 2: Model 1 + body mass index, systolic blood pressure, hypertension medication use (no, yes), total cholesterol, HDL, triglycerides, education (less than high school, high school/vocational school, college or higher), smoking status (current, former, never), drinking status (current, former, never), history of parental diabetes (no, yes), $eGFR_{cr}$, and log albumin-to-creatinine ratio

Table E-3. Adjusted hazard ratios and 95% CI of categories of hyperglycemia and 1,5-AG concordance for risk of incident diagnosed diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality, n=6,644

Categories of Hyperglycemia and 1,5-AG concordance	Diagnosed Diabetes				CKD		
	n	Events	HR (95% CI) Model 1	HR (95% CI) Model 2	Events	HR (95% CI) Model 1	HR (95% CI) Model 2
True Negative (TN)	5681	1166	1 (REF)	1 (REF)	1112	1 (REF)	1 (REF)
False Positive (FP)	220	59	**1.41** (1.09, 1.83)	**1.52** (1.17, 1.97)	39	0.83 (0.60, 1.15)	0.83 (0.61, 1.15)
False Negative (FN)	610	409	**6.31** (5.62, 7.09)	**4.90** (4.35, 5.52)	141	1.16 (0.97, 1.38)	0.92 (0.77, 1.10)
True Positive (TP)	133	116	**16.5** (13.6, 20.1)	**11.9** (9.70, 14.6)	42	**1.68** (1.24, 2.29)	1.30 (0.95, 1.79)
	CVD				**All-cause mortality**		
	n	Events	HR (95% CI) Model 1	HR (95% CI) Model 2	Events	HR (95% CI) Model 1	HR (95% CI) Model 2
True Negative (TN)	5681	653	1 (REF)	1 (REF)	1466	1 (REF)	1 (REF)
False Positive (FP)	220	27	1.04 (0.71, 1.53)	1.13 (0.77, 1.66)	55	0.88 (0.68, 1.16)	0.85 (0.65, 1.12)
False Negative (FN)	610	103	**1.43** (1.16, 1.77)	1.19 (0.96, 1.48)	219	**1.25** (1.09, 1.45)	**1.21** (1.05, 1.40)
True Positive (TP)	133	25	**1.55** (1.04, 2.32)	1.24 (0.83, 1.87)	48	**1.34** (1.01, 1.79)	**1.37** (1.02, 1.84)

Bold indicates $p<0.05$

Model 1: age, sex, race-center

Model 2: Model 1 + body mass index, systolic blood pressure, hypertension medication use (no, yes), total cholesterol, HDL, triglycerides, education (less than high school, high school/vocational school, college or higher), smoking status (current, former, never), drinking status (current, former, never), history of parental diabetes (no, yes), $eGFR_{cr}$, and log albumin-to-creatinine ratio

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Presentations

Moderated Poster: "1,5-anhydroglucitol to Identify Older Adults with Diabetes at Risk of Hospitalization and All-cause Mortality," American Heart Association Scientific Sessions; New Orleans, LA, March 2018.

Moderated Poster: "Diabetes and Trajectories of Estimated Glomerular Filtration Rate (eGFR) in the Atherosclerosis Risk in Communities (ARIC) Study," American Diabetes Association; San Diego, CA, June 2017.

Oral Presentation: "Comparative prognostic performance of definitions of prediabetes: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study", American Heart Association Scientific Sessions (Hot Off the Press); Portland, OR, March 2017.

Moderated Poster: "Performance of 1,5-anhydroglucitol compared to the oral glucose tolerance test and fasting glucose for identification of diabetes in the community," American Heart Association Scientific Sessions; Portland, OR, March 2017.

Poster: "Comparison of the prognostic value of 1,5-anhydroglucitol and the oral glucose tolerance test in the Atherosclerosis Risk in Communities Study," American Heart Association Scientific Sessions; Portland, OR, March 2017.

Moderated Poster: "Age-related changes in hyperglycemia: Comparison of different biomarkers," American Diabetes Association; New Orleans, LA, June 2016.

Oral Presentation: "Comparative Prognostic Performance of Different Definitions of Prediabetes in ARIC," T32 NHLBI Trainee Session, American Heart Association Scientific Sessions; Phoenix, AZ, March 2016.

Moderated Poster: "Comparative Prognostic Performance of Different Definitions of Prediabetes in ARIC," American Heart Association Scientific Sessions; Phoenix, AZ, March 2016.

Awards and Fellowships

- NIH/NHLBI Pre-doctoral Training Grant in Cardiovascular Disease, 2014-Present
- American Heart Association, EPI Early Career Travel Grant, 2018
- Johns Hopkins University Bloomberg School of Public Health, Department of Epidemiology, Student Travel Support Fund, 2017
- Dean's List, University of Pennsylvania, 2007-2010
- Intercollegiate Women's Lacrosse Association Academic Award, 2009
- Varsity Women's Lacrosse (Ivy League Champions and NCAA Division I Final Four 2007-2009)

Professional Activities

- Reviewer: Atherosclerosis Risk in Communities Study (Internal Manuscript Review Process), 2016, 2017
- Co-reviewer: New England Journal of Medicine, 2017; Lancet Diabetes and Endocrinology, 2017; Diabetic Medicine, 2017; Clinical Chemistry, 2016; Journal of American College of Cardiology, and Nutrition, Metabolism, and Cardiovascular Diseases, 2016
- Member, American Heart Association, 2014-Present